The Journal of
Nervous and Mental Disease

Vol. 124, No. 1 JULY 1956 Serial No. 895

TRENDS IN BIOLOGICAL RESEARCH IN SCHIZOPHRENIA[1]

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The last few years have brought forth a serious of new attacks on the age-old problem of schizophrenia, that stubborn disorder which accounts for so much sickness in our field of medicine, and which is with us wherever we turn our heads. In our more optimistic moments I am sure that we feel that the heavy artillery of Science has now been drawn up against this enemy. If the fire is heavy and well directed, we may hope to have the satisfaction of being, if not participants, at least spectators at the kill. Even the lowliest of military men know, however, that artillery alone does not win battles. Much more needs to be done to gain the contested ground.

Investigative efforts in schizophrenia are scattered over a wide front. The most tangible advance has been made in the clinical therapeutic sector. In addition, fronts are established in "model psychosis" inquiry, in chemical sectors of schizophrenia including its experimental models and the drugs now being used in treatment, and in the neurophysiologic phenomena which parallel these chemical changes.

The study of drug therapy is schizophrenia was begun accidentally and pragmatically by alert clinicians. Reserpine was introduced as a hypotensive agent, but when it became evident that its hypotensive effect was central and at the highest level of psychic control, clinicians began to study the drug in the therapeutic area where its parent, *rauwolfia serpentina*, had been employed in the Orient (57). Chlorpromazine was studied first as an antihistaminic, but it did not accomplish very much therapeutically in this field. It was found to be of value in the control of the vomiting of pregnancy, in gastric neuroses, in certain pain syndromes (52), and in the psychoses, as French clinicians felt their way along the dark corridors of therapeutic trial and error.

You are acquainted with the results to date (24, 56). In state hospital settings these drugs have produced a windfall of improvement in disturbed patients. The need for repeated palliative electroshock measures to keep overactive patients at a reasonably good behavior level has been minimized, and the doors of many a closed ward have been opened for the first time. Effects are most impressive in lowering the level of psychomotor overactivity in schizophrenic patients; but hyperkinetic patients with neurological syndromes such as epilepsy (5, 59), cerebral palsy (9), mental retardation (2, 8, 47), and to some extent those with senile psychoses (48), respond as well. In addition, chlorpromazine, perhaps the more hopeful of the two drugs, appears to be capable of controlling the psychomotor excitement of mania. Where pressure of psychic and motor activity is not present, the drugs are of much less value. As with most of the therapeutic attempts in schizophrenia in our generation, if these drugs are applied before the pathologic pattern of thinking and acting becomes set, i.e., within the first year of illness, the chances for recovery increase greatly.

The drugs are not easy to employ in an office setting in patients who are trying to compete socially and economically with their so-called normal fellows. Apathy, dizziness, somnolence and a vague lowering of the *elan vital*, the vital force and drive which is one of the most admirable qualities in the human personality, sometimes provoke the demand for lowering of dose levels to the point of ineffectiveness and even abandon-ment. In the case of chlorpromazine, in addition to the relatively infrequent side-reactions of photosensitivity, skin rash, jaundice, and agranulocytosis, our women patients, who all seem to want to attain the half-starved silhouettes of their sisters from Hollywood, can be sharply critical of the weight gain the drug often produces. In addition to nasal stuffiness, profound and alarming depressive reactions may arise during reserpine therapy, especially if it is prolonged.

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[1] Presidential Address, Society of Biological Psychiatry, April 29, 1956, Chicago, Illinois.

Both chlorpromazine and reserpine have produced parkinsonism. This is something new in the world. Neurologists have searched in vain for a way of duplicating this syndrome experimentally in animals. The next best thing is the production of parkinsonism under controlled conditions by drugs in humans. Will this bring us any closer to the solution of the riddle of clinical parkinsonism? Himwich (28) has turned his attention to this problem.

Other drugs have crossed the horizon recently in the treatment of schizophrenia. Azacyclonol, or Frenquel, is an exasperating in-and-outer and appears to be more likely to succeed (12, 13, 14, 45, 46) in delirioid and toxic psychoses than in the bulk of the schizophrenic group. Chlorpromazine without the chlorine atom in its molecule, or promazine (21), also has been under study lately, and preliminary information discloses that it may also prove of value in the more acute group of dissociation syndromes. The fact that chlorpromazine saw the light of day as an antihistaminic has turned attention to the possibility that other antihistaminic drugs may prove of therapeutic value in schizophrenia. I know of two which are under clinical study at present, and perhaps there are many more. The report on one, Doxylamine, is being made at this meeting (22).

Where do we stand in these clinical pharmaceutical investigations? Where are they going? The most skeptical must be driven to the conclusion that a new type of chemotherapy has been established, and that the day of the ataractic drugs, as I (15) have called them, is here. None may be called the ***therapeuticum magnum***. All have their limitations and their drawbacks. We may be sure, however, that the pharmacologists and the synthetic chemists are hard at work on yohimbine indoles of which reserpine is a member, on phenothiazines from which chlorpromazine and promazine are derived, and on the piperidyls, the family from which Frenquel comes, among others. A great deal of juggling, shifting and altering of formulae to produce more effective drug responses is going on. The chemists can almost make these and other compounds to order and at will. The pharmacologists have a much harder job in screening the creations of the chemists. To date there are no established sorting methods in the animal to predict that this or that compound will have the power to clear the muddled sensorium of a schizophrenic human, although Marrazzi's studies (26) in this field are hopeful. Despite this area of ignorance that the chemists will make, the toxicologists will test and the clinicians will try more of these drugs. A breach has been made in the wall, and the attack from this quarter will quicken.

One piece of information has come to me from these drug studies which is making me change an intellectual prejudice of mine. In the past I held the basic idea that there was a spectrum of disorders which extended form schizophrenia through schizo-affective reactions to melancholia and/or mania, and that some common etiology would finally explain all these functional psychotic disturbances. The fact is that these drugs set the depressions quite apart from the other disorders, and the effect of the drug which appears to be of value in mania, i.e., chlorpromazine, seems to be only to hold it in check while the attack runs ts course. This makes me begin to change my thinking. I am now prepared to believe that the ultimate biological etiology for the mood psychoses may turn out to be totally different from that of the schizophrenic group. At least this inference, which can be drawn from the therapeutic drugs studied to date, seems to have respectability.

The next investigative front in schizophrenia is that of its experimental models. For more than a half century, mescaline has been known to cause a temporary psychosis of schizophrenic type, and a rich literature (3, 29, 35, 36, 41, 53) on this subject has been compiled. When LSD's ability to mimic schizophrenia (54, 55) was reported in 1947, a quickening of interest in the whole subject of model psychoses began to take place. Other psychotomimetic drugs have been sought in the world of botany and in the chemical laboratory. Anthropologic lore has uncovered the practices of men who have searched throughout history for what Aldous Huxley (33) has called the "other-worldly" experiences produced by hallucinogenic seeds (43), mushrooms (6, 16, 51), roots (49) and plants. There are 13 "phantastica" listed among the botanical products used by the Mexican Indians alone (25). Australian aborigines fermented a species of pine nuts in urine, and when they ate them, a veritable delirium tremens resulted (7). Plants of the rue family, containing harmines, have also been employed to produce temporary psychotic dissociations. The Saskatchewan group of investigators has studied metabolites of adrenalin (30, 31) in this connection. The list could be enlarged. Huxley's (34) recent "Heaven and Hell" is a searching inquiry into the reasons why men have done these things.

The chemistry of these agents is either totally unknown or is only partially understood. Some of them seem to contain bufotenine as at least one of their constituents, as Fish and Horning (23) are reporting at this meeting. This compound is capable of producing a short-lived LSD or mescaline-like model psychosis when injected intravenously in man (17, 18). Studies of its oral effects are planned. Bufotenine is an indole, as is LSD, adrenochrome, adrenolutin, yohimbine, ibogaine and harmine. Mescaline probably metabolizes into an indole after its ingestion. We are hearing a report at this meeting by W. K. Sherwood (50) that another indole which he makes in his laboratory, and which he is calling "BGE" (blue-green to Ehrlich's Reagent) until he can identify it chemically, causes him to become psychotic when he inhales it.

Are all indoles hallucinogenic for man? Emphatically, no! Conversely, are all hallucinogens indoles? Again, no! Cannabis is not (1), the belladonna derivatives are not, the opiates are not, nor are the bromides among others. Yet they can all produce psychotic dissociations which have much of the look and feel of schizophrenia while they are in progress. This poses a new program of inquiry for the chemists. Is there a common denominator in all these things? We cannot hope for a quick answer, but we can expect pieces of it to be revealed as laboratory work progresses. Indole chemistry is under intensive study and review. These compounds derive from tryptophan and perhaps from tyrosine in biological systems. They are extremely reactive, changing quickly from one to another. All the stations along their metabolic pathways are not known, nor are the enzymatic troubles they may encounter along the way.

One of the non-hallucinogenic indoles which has received a great deal of study of late is 5-hydroxy-tryptamine, or serotonin. Udenfriend (58) has reported on it at this meeting. The exact function or functions of this neurohumoral agent in normal human physiology await clarification. Do the ataractic drugs exert their influence against this compound? Is serotonin the root and stem from which endogenous hallucinogenic compounds, which in turn poison our central nervous systems, arise? As an indole is it a chemical changeling like many of its fellows? Can serotonin be perverted into a compound or compounds which compromise the biological economy of the central nervous system and thus render us psychotic? If so, what are the enzymatic keys which unlock this Pandora's box of troubles? Or do chemical troubles arise at a less complex level? Tryptophan is an amino acid derived from the tryptic digestion of proteins. There has been a question about the first step of its metabolism to formyl kynurenine (10). Is this perhaps the site of trouble as Sherwood's work suggests? Are all the speculations about disturbances in indole chemistry a tempest in a teapot? Is the etiology of schizophrenia to be found in a quite different place? These are but a few of the questions which are undergoing intensive laboratory study.

No clinician needs to be reminded how difficult it is to make the diagnosis of schizophrenia because of its varied manifestations. There has been a long-standing conviction on the part of many physicians who see these people at the bedside that schizophrenia is not a disease, but rather a collection of disorders having similar manifestations. A little more than a century ago fever was a disease. The fevers are now sorted out etiologically, thanks to the bacteriologists, and their treatment proceeds along more enlightened lines. The attempts to break the schizophrenias up into etiologic groupings of this kind have been a recurring hope in medicine. Meduna's concept of oneirophrenia (40) is the most recent example of the sorting out of a piece from the whole. This kind of compartmentalization cannot proceed without laboratory aids since the laboratory is the place to study and confirm the etiology of most human ills.

For some years Macht (37, 38) has contended that various diseases, among them schizophrenia, are associated with a presumed toxin in the circulating blood. He reports that the blood serum of schizophrenic patients inhibits the root growth of seedlings of *Lupinus albus*, an Italian forage plant. This work has remained something of a medical curiosity, and has not been pursued widely. More recently, another type of biological toxicity test for schizophrenia has been reported. The Schizophrenia Research Group in Saskatchewan, Canada, reported last year that schizophrenic serum was capable of killing the mitotic cells in a tissue culture preparation, but that the test was not wholly specific. They have used the L-strain fibroblast, a standard cell culture derived from the subepithelial derma of the mouse. Hoffer, a member of that group, reports (32) further at this meeting on this presumed toxin. This should stimulate the speculative mind. Is this a potential laboratory test for schizophrenia, or for a part of schizophrenia? Can some determined analytical person dig out the chemical nature of such a toxin? Can some hunch-player assume its formula and find the nature of Hoffer's toxin that way? Is there a similarity between Macht's and Hoffer's findings? Both of them note a disturbance in growth. The plant growth hormone, or auxin, is said to be indoleacetic acid. To this may be added Sherwood's observation at this meeting that the ataraxics—reserpine, chlorpromazine and azacyclonol—all inhibit the development of sea-urchin embryos, presumable by interfering with normal indole growth compounds. Does this lead once more to the thought of a perversion of indole chemistry in the etiology of schizophrenia? This is a provocative line of inquiry, and we may hope for more about it in the future.

If we submerge our intellectual reservations about many of these matters concerning the trends in biological research in schizophrenia, and if we make a series of assumptions reluctantly, we are still faced with a major problem. Let us assume that the tranquilizing drugs now at hand and on the way are truly ataractic, that they produce freedom from confusion and peace of mind by direct attack on the schizophrenic pathogen in the central nervous system. Let us assume that the psychotomimetic drugs actually mimic clinical schizophrenia, and that the chemical dynamics of the model and the real thing are similar. Let us assume that an endogenous toxin or toxins brewed within us through metabolic error forge the key to the riddle of schizophrenia. Let us assume that one of the attractive possibilities is that an indole or a group of indoles are the etiologic toxic agent which brings this about (19, 20). Even if we grant all that, we still have a major hurdle to jump. Why should such unproved toxic agents produce schizophrenic symptoms? Why not sleep, coma, convulsions, paralysis, or some other manifestation of sickness in the nervous system? It is easier to pose this question than to answer it, because it lays open the whole subject of the neurophysiology of schizophrenia, about which there are much speculation and little knowledge.

A group of diverse findings prompt me to wade timorously in these muddy waters. The comparison weaves throughout Bleuler's rich clinical accounts (4) of schizophrenia between the symptoms he encountered and the manifestations of dreaming and similar crepuscular states between wakefulness and sleep. The remarkable experiments of Hebb (27, 42) in the production of schizophrenia-like symptoms in normal subjects placed in an environment of almost total sensory constriction are worthy of comparison with states of semi-sleep. Next comes Pavlov (44), who spent the last decades of his life studying the behavior of dogs in the interland between alertness and sleep. In states of this kind, which he called hypnosis clinically and partial inhibition of the hemispheres physiologically, he noted apathy, negativism, catatonic posturing and repetitive stereotyped movements, as well as an abolition of the conditioned responses which the dogs had built up. He noted perversions in behavior in which both weak and strong stimuli produced the same degree of response, which he called the phase of equalization. He noted times when weak stimuli produced greater response than strong ones, his paradoxical phase; and he noted other occasions when an excitatory stimulus provoked, instead of the expected excitatory response, its opposite or inhibition. This he called the ultraparadoxical phase. He regarded all these as varying levels of partial inhibition in the hemispheres. He likened these unexpected and therefore illogical behavior responses to schizophrenia in man, and drew a series of provocative analogies.

The work of Marrazzi (39), Evarts *et al.* (11), and of other workers in their field on the partial inhibition of monosynaptic transmission in experimental animals by hallucinogenic drugs seems far afield from Bleuler and Hebb and Pavlov. It is noteworthy, however, that all of them come to speak of partial inhibition of neural activity. Impedance would be a better word. The workers with psychotomimetic drugs report an impedance in the time and in the volume of trans-synaptic transmission by these drugs.

Let us make a simple analogy. The speed, the precision and the grace of a double play in baseball is a thing of beauty which approaches a perfect example of coordinated activity among humans. It has been helpful to me to compare this swift chain-reaction play with neural transmission at the higher levels. The ball, as it moves from pitcher to batter to one infielder after the other, may be likened to the changing, shifting nerve impulse. The split-second handling of the ball by each player along the chain may be regarded as synaptic transmission, and the cheers (or boos) of the spectators may be compared to the emotional side-effect of such a neural circuit-in-action.

But if a double play ball were hit, and if the infield were to play it with impedance of the expected time and magnitude of response, it would become meaningless, illogical and ludicrous. If the ball were fielded slowly and apathetically and lobbed from base to base instead of being thrown with maximum precision and speed, all runners would be safe, and the fans would scream with outrage. Furthermore, all downstream neural responses would be altered, i.e., the whole course of the game would change. If this same sort of disturbance in the time and magnitude of response kept occurring through subsequent innings of the game, both on the part of offensive and defensive players, the result would not be baseball but a buffoonery of the game, a colossal illogical shambles of behavior. Eighteen men exhibiting a partial impedance of their responses in time and volume would be playing hebephrenic baseball, and if they slowed up quite a bit more, they would be playing catatonic baseball.

Rather than carry this analogy further, let us pursue the contention which provoked it, that of impedance of neural transmission at the synapses. It is becoming more clear that the delicate balance between excitation and inhibition of neural impulses, mediated at the synapses by cholinergic and adrenergic substances, is the very stuff of all nervous activity, including all thought and behavior. The presumption here, based on fragmentary neurophysiologic findings and a good deal of guessing, is that schizophrenic symptoms arise when this balance shifts part-way in the direction of the adrenergic side, the side of partial inhibition, the side of impedance, the side of slowing and partial suppressing of the total neural activity rather than its total blocking or abolition.

Where do the eruptive, the repetitive, the overactive symptoms so often encountered in schizophrenia, such as stereotypy, hallucinations, delusions and psychomotor excitement, fit into such a construct? I feel certain that we all have hallucinations and delusions on occasion, just as we have tendencies toward stereotypy and psychomotor overactivity. Those of us who are in good health have a constant play of corrective signals, or counter-excitations, which dampen down and vitiate these patterns of morbid neural activity. When states of impedance exist at the synapses, these balancing counter-mechanisms fail, and excitatory fields continue to fire off in a more or less random and independent way. Pavlov would call these sore spots in the cortex, Bleuler would call them the spontaneous internal activity which occurs in dream states as well as in schizophrenia, and Hughlings Jackson might call them release phenomena due to the lack of higher cortical control.

I am certainly not proud of these wayward excursions into higher level neurophysiology.

There are great gaps in the argument, and it is far too fragmentary. It is presented because it seems to express the trends of current thinking in the neurophysiology of schizophrenia, and seems to fit in with the newer knowledge being developed about the mode of action of psychotomimetic drugs.

William James is credited with the statement that psychology cannot be explained in terms of psychology. Despite his admonition, a great many dedicated students of schizophrenia and other psychiatric disorders have occupied the first half of the twentieth century with inquiries of that kind. A welcome increase in interest in the mentally deranged and a deeper sympathy for their plight have come from these studies, but the morbidity rate remains sky high. The second half of our century finds us in a swing back to a more orthodox type of medical investigation. A multidirectional attack in the field of biological research in schizophrenia is in progress. It has seen the beginnings of a new chemotherapeutic attack, a clinical interest in experimental models, a broadening of chemical inquiries into the disease itself, its experimental models and the drugs in use against it, and the gropings toward an understanding of the neurophysiologic basis of its manifestations. It will be interesting to sit by and see where this all leads.

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A LONGITUDINAL STUDY OF CHANGES IN EEG FREQUENCY PATTERN AS RELATED TO PSYCHOLOGICAL CHANGES[1]

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Routine analysis of electroencephalograms has demonstrated in the past that there are significant relationships between such psychological factors as aggression (3) or anxiety (1) and certain EEG patterns or types. It has been demonstrated also, from many sources, that the background EEG patterns in psychopathology are different from those seen in individuals with relatively normal psychological functioning (4). In our own studies analysis of EEG frequency patterns has shown, even more definitely, that there is a significant correlation between psychological criteria and type of EEG pattern (5, 8).

Since such differences exist, it has now become of interest to discover whether these individual frequency patterns are inherent in their basic EEG structure and thus perhaps are relatively inflexible in terms of severity of functional psychiatric disturbance or whether, during the development of mental disorder, a functionally related change in EEG frequency pattern may occur. It is well known that, once the adult EEG pattern has become established in a normal individual, it remains relatively fixed unless organic changes intervene. But, on the other hand, it is known that temporary fluctuations in EEG pattern are easily induced by stressful situations (4) and, in the monkey and cat at least, that an EEG pattern can be readily conditioned (7). Furthermore, it is recognized that relative stability or instability is a characteristic of specific EEG patterns, that with a high percentage alpha activity is more stable and less responsive to stimuli such as hyperventilation or flicker than that of a predominantly beta activity with an intrinsic dysrhythmic quality. It is this latter, less stable type which is found in increased amounts among patients in psychiatric hospitals and in children with disorders of behavior. Since there are many factors in the EEG pattern which can be observed by frequency analysis which are undetectable in the routine EEG examination, this method has been used for the present longitudinal study in which EEG and psychological criteria have been examined and compared in 70 mental hospital patients and 27 controls.

METHOD

During a period of about one and a half years, all suitable first admissions to the Crease Clinic of Psychological Medicine, Essondale, British Columbia, have been examined. Suitability, as defined by the project, included all patients between the ages of 12 and 30 inclusive, with an I.Q. of over 80, who were sufficiently cooperative to be able to take the psychological tests, and who had not had any form of shock therapy for the preceding four months. The Crease Clinic is the unit of this Mental Hospital to which the relatively mildly disturbed patients are admitted for treatment, the maximum stay being four months, and the incidence of discharge back to previous home situations being about 80 per cent. The subjects were, therefore, relatively mildly disturbed with relatively recent onset of their illness. About half were voluntary committals. They were selected because of these facts. It was felt that in such patients the origins of their disturbances might be more easily appraised than in an older and more severely disturbed group. About half were schizophrenics; the other half less severely disturbed people having, usually, some evidence of neurotic symptoms or of disorders related to aberrant social performance.

All 70 patients were examined as soon after admission as was possible and again, in 47 instances, after about one month's interval. Of these 47 patients many had three to five EEGs recorded although psychological tests were given only twice, the third to fifth EEG tests being given during second to fourth months after admission. All those diagnosed as schizophrenics received insulin coma treatment between the first and second tests. The other

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[1] Aided by a Federal Mental Health Grant and by the Mental Health Services, Province of British Columbia, Canada.

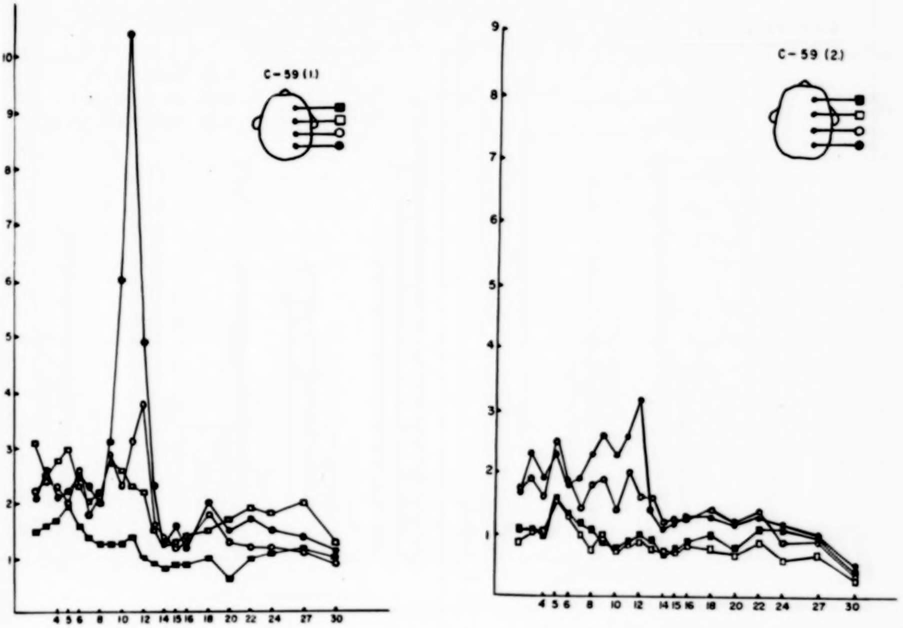

FIG. 1. Graphs of EEG frequency pattern from a normal control 1) relaxed and 2) in alpha minus, alerted state.

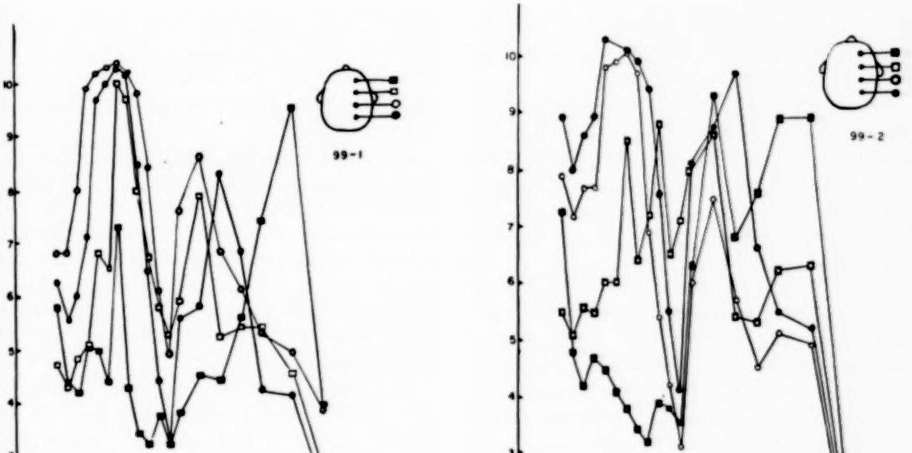

FIG. 2. Two frequency graphs from the EEGs of a single patient. Records taken one month apart.

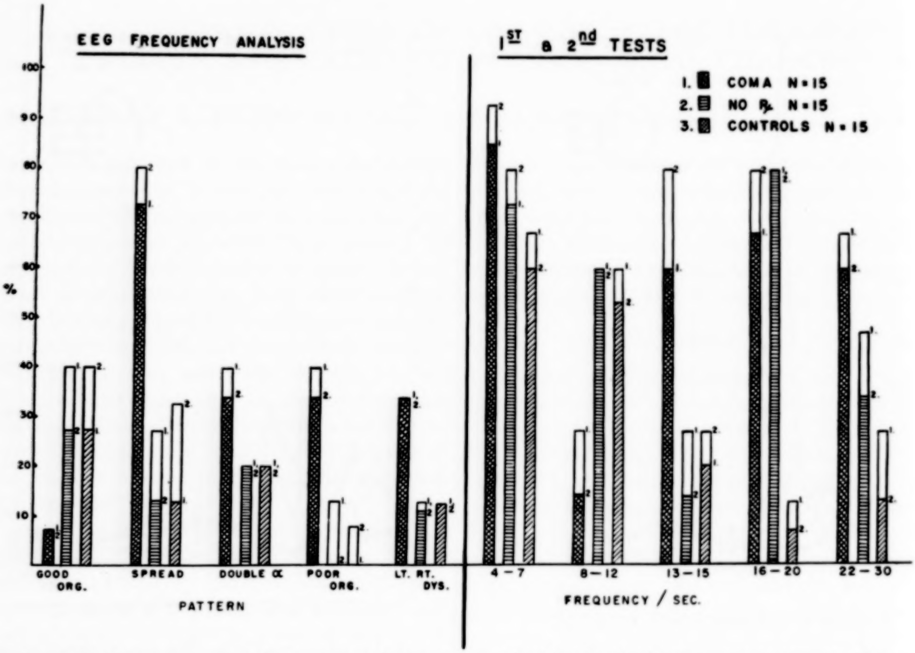

FIG. 3. EEG frequency analysis of average characteristics; 12 schizophrenics having coma treatment; 15 non-psychotic having no physical treatment; and 15 normal controls. Two tests, each individual, one month apart.

group of non-psychotic patients had no form of physical treatment beyond the occasional sedative. Barbiturates were not given.

The 27 control subjects were recruited from the Hospital and Medical School staff. They were matched, roughly, with the patient group as to sex, age and educational achievement. Each control subject had two EEGs and two psychological tests only, given at about a one-month interval.

EEG recordings were made, both bipolar and monopolar, according to a conventional routine on an eight-channel Grass electroencephalograph. In addition a frequency analysis of the EEG pattern was always made, using an Offner Frequency Analyser, Model III. A routine recording by this means was made as has been described in detail previously (5). Subsequently, measurement of the height of the analyser pen deviations was made and a graph drawn in which the frequency patterns from various cortical areas were superimposed (figs. 1, 2).

Psychological examinations utilized the Wechsler Bellevue, Rorschach and Bender-Gestalt tests which had been shown during previous years to produce useful patterns for EEG correlation (8). Retest was carried out with due regard for the factor of repetition of test situation.

An initial interview with each subject, patient or control, was also held in which an appraisal was made of his present situation and information gathered as to his past family and personal history, educational achievement and success in adult life. A tentative psychiatric diagnosis was then made which was later compared with that given on discharge by the clinical staff of the hospital.

The psychologist then evaluated individual tests (from which a report was sent to the clinical record of each patient). The second author evaluated the EEGs according to the routine method of appraisal and then the frequency graphs. A scale of ten factors, explained elsewhere (7), was used for analysis of EEG frequency pattern. Half of these were indices of prevailing EEG rates, and the other half, of pattern interrelationships as shown in figures 3 and 4. Good or poor organization,

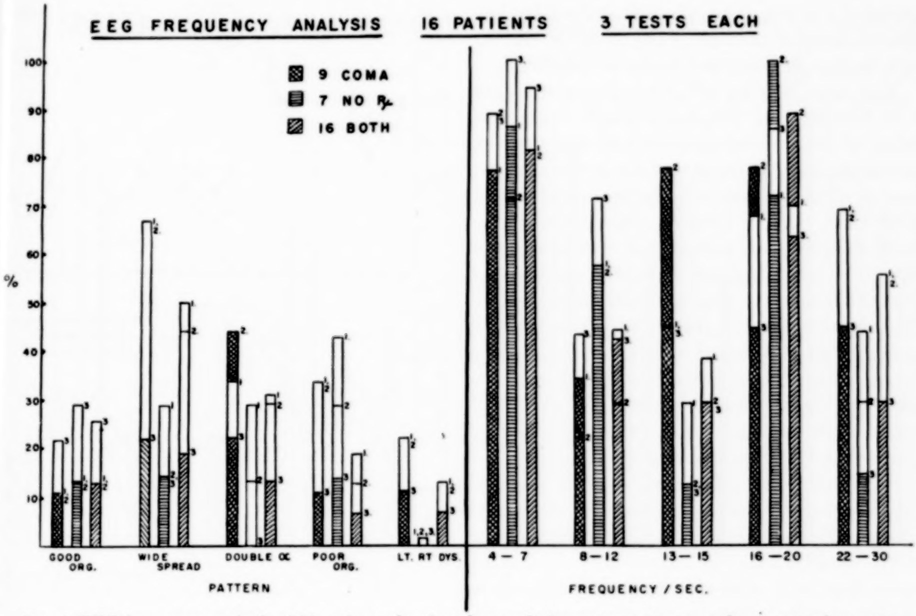

FIG. 4. EEG frequency analysis of 16 patients showing changes in frequency pattern on three successive tests.

double alpha peaks, wide spread of total activity between recording areas, and left-right dys-synchrony were factors which had been found on previous examination of a larger series to be significantly related to psychological diagnosis.

Eventually, when these examinations had been completed for the entire series, psychologist and psychiatrist together attempted to appraise interrelationships with the following results.

DATA

Frequency pattern and clinical status. Earlier analyses of frequency patterns of a larger group of subjects had shown that the most outstanding difference between the EEG patterns of the psychiatric patients and their normal control equivalents was in the order or disorder existing between frequency patterns from different areas of single cortex. In figure 1 is shown the frequency pattern recorded from a normal individual having a high per cent of alpha activity. The amount of activity for each recorded frequency changes in more or less coordinate fluctuations such that the over-all pattern shows a rhythmic course from 4 per sec. to 30 per sec. at each cortical area. This appears in both graphs of figure 1, which are from the same subject, the first during a relaxed period and the second during an alpha-minus, alerted state. They are examples of the type of pattern which predominates in normal subjects. Figure 2, in contrast, shows two frequency graphs from a schizophrenic subject. Characteristic of this type of record is the poor coordination among recording areas, the total high energy pattern, and the presence of large amounts of energy in the abnormal wave-rates above and below the alpha band.

Figure 3 is a histogram of these frequency characteristics in three groups of subjects, each selected, in chronological order from the total subjects in its category according to psychological characteristics and clinical history and without regard for EEG pattern. The first group comprised 15 patients who were undoubtedly schizophrenic and who had coma insulin treatment. The second consisted of 15 who were without doubt non-psychotic and who had no physical treatment. Fifteen "normal" controls were then selected from the 27 normal subjects as those who not only had no personal history of psychological disorder but also no familial pattern of psychopathology or of a broken or disturbed home in childhood.

The most striking difference shown in figure 3 is between the frequency graph characteristics of the normal controls and those of the schizophrenics. In most instances those of the non-psychotic subjects lie between these two. Less than ten per cent of schizophrenic subjects showed good and regular organization of EEG pattern although 30 to 40 per cent of the other groups showed such organization. The schizophrenic group had significantly greater spread between recording areas, double alpha peaks, poor organization of EEG pattern and left-right dys-synchrony. The abnormal rates, both theta and beta, were also definitely greater in the schizophrenic group.

In figure 3 the difference between first and second test frequency characteristics is also shown. The number 2 in each unit signifies the level obtained at the second test. It can be seen that with time the pattern improved in many factors although in many others the changes are slight and only, perhaps, suggestive. In figure 4, however, more pronounced changes of the same order appear. This figure shows the per cent of frequency characteristics present in a first, second and third EEG test in 16 patients. The interval between first and second test was one month, that between first and third varied between two and four months, the final test being given at the end of the period of recovery on the ward and just before discharge. In this graph the factors on the left hand side, good organization, good alpha activity, have increased during hospital stay while factors related to poor inter-area organization have decreased. Thus, the averages of the last records of these patients showed less fast activity and far less spread of frequency pattern than did the first. The third tests are nearer the control levels.

This improvement in frequency organization is borne out by data shown in figure 5 in which the standard deviation of the various wave frequencies has been estimated from actual measurements of frequency record of the same cases. We have reported previously (8) that the standard deviations of given wave forms in a group of schizophrenic patients were greater than those of a) a prison population and b) a normal control group. Figure 5 shows that, on repeated examination, the standard deviations of both schizophrenic coma patients and the untreated non-psychotic group decrease, particularly in the rates which are abnormal, thus approaching the lowered variability found previously in a control group (8).

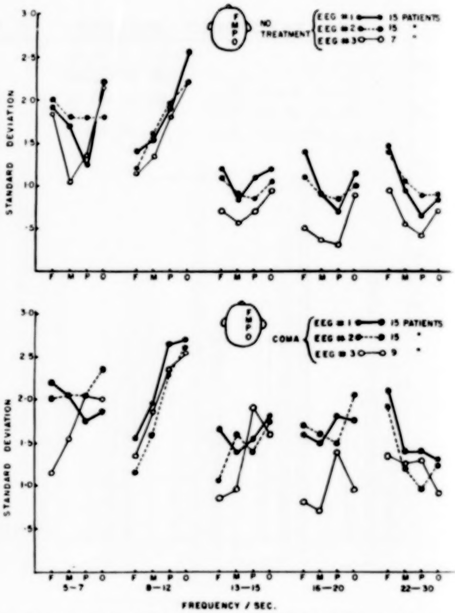

FIG. 5. Standard deviation of EEG frequencies, on three successive tests. Two groups of patients; schizophrenics having coma treatment and non-psychotics having no physical treatment.

From these data it can therefore be suggested that the types of EEG pattern known to be more prevalent among the psychologically disturbed than among the normal are related to inter-areal frequency dys-coordinations, that these are to some degree variable, and that they are possibly affected by the present status of the patient and by his recovery.

Frequency pattern and personality structure. With this in mind, we proceeded to further analysis of psychological and EEG factors. A more detailed report of the changes as seen in the psychological examinations will be given elsewhere as will an analysis of EEG changes. As reported before single psychological characteristics such as anxiety have appeared related to certain EEG patterns, but in the present study, with repeated interviews of the pa-

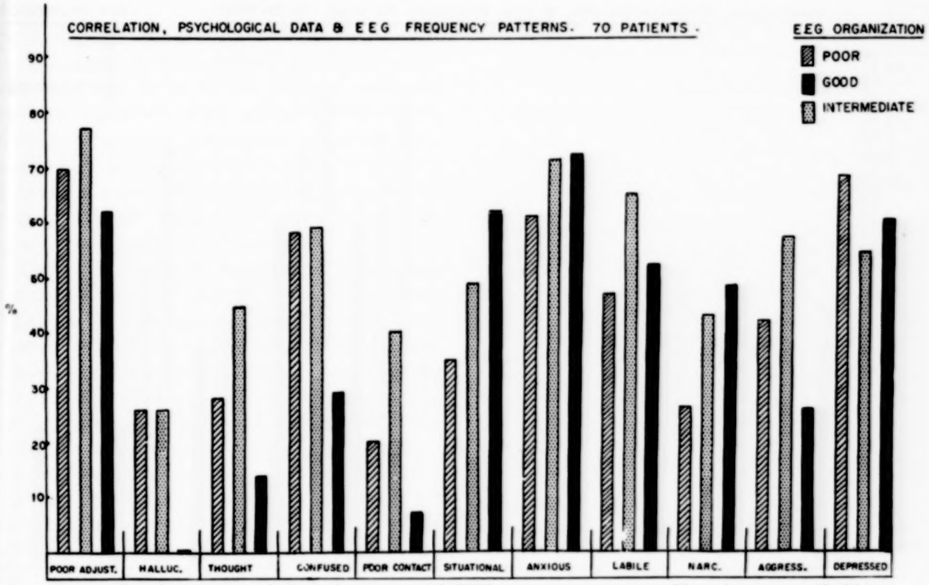

FIG. 6. Correlation of psychological pattern with EEG frequency pattern in 70 patients, ages 12–30.

tients, both authors became certain that an over-all personality pattern using psychological test material to supplement the case histories might prove more useful. For instance, after many patients had been tested, it appeared that the "worst" and least well-coordinated EEG frequency patterns were always associated with an acutely disturbed patient, rather than with one who had had a more slowly developing chronic sequence leading to hospital admission. We therefore re-did our analysis of significant factors, the psychologist working separately from the electroencephalographer, each then sorting data according to new and more general terms.

The EEG frequency patterns were sorted as to whether they were "good" and well organized as are those of figure 1, or poorly organized as in figure 2. An "intermediate" group lay between. On a scale of 3 the good records were "ones" and the poor "threes". All records were sorted in this way, and eventually those whose frequency graphs had remained "unchanged" during two to five recordings were compared with those which had become "worse" or "better". Similarly, the psychological characteristics were classified as slight, intermediate, or marked. Fifteen categories were tried in this way of which 11 were finally found to be useful in the appraisal as shown in figures 6–8.

Here the psychological criteria have been arranged according to the type of disorder in which they were most apt to appear. It should be remembered from this point on that some criteria had to be evaluated qualitatively on a different scale for the control group than for the patients. Most notably this obtained in the category "*adjustment to environment*". The adjustment of a patient in a mental hospital, although relatively "good" not "poor", was in either case far worse than the adjustment of a control who might be also relatively "good" or "poor". The next three categories were those appearing either entirely or largely in schizophrenic patients. *Hallucinations*, as encountered clinically, *thought disturbances*, as shown by tests, and *confusional conditions*, usually shown in both ways, were all common among schizophrenics. *Poor contact* with the examiner also was found very largely among the schizophrenic group. Situational was the term given to those patients who had been admitted to the hospital with some immediate precipitating factor in their history. *Anxiety*, *aggressions* and *depression* were measured by

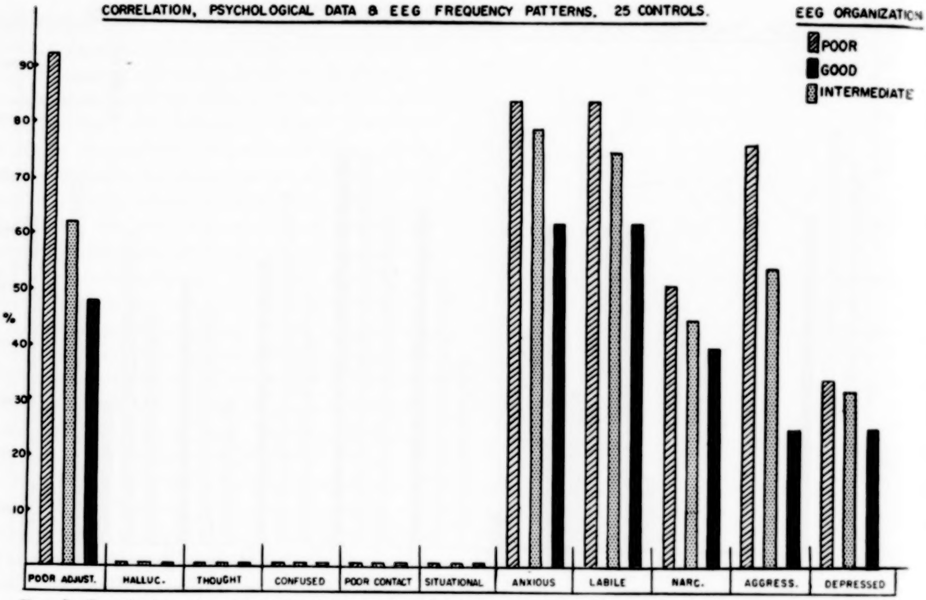

FIG. 7. Correlation of psychological data and EEG frequency patterns in 25 normal control subjects, ages 18–30.

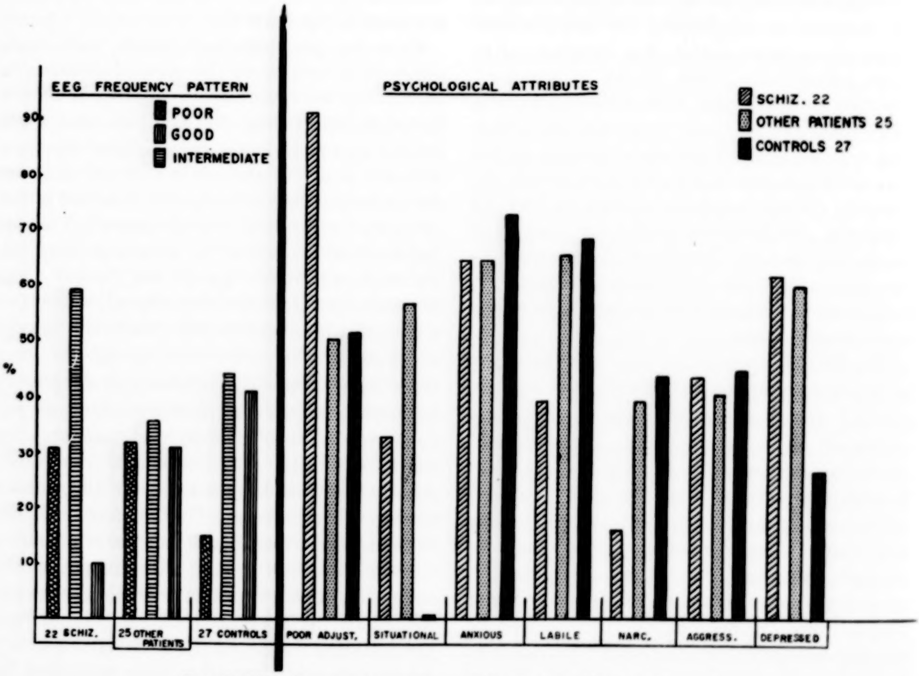

FIG. 8. EEG frequency pattern as related to psychiatric diagnosis.

psychological test criteria and behavioral appraisal. *Lability*, also defined psychologically, was the term given to the pattern exhibited by the immature and unstable individuals showing fluctuant emotional behavior patterns. *Narcissism* appeared as another entity in individuals unable to adjust to environment because of self-concepts which diverted adequate relationships to others.

The data shown in figures 6–8 have been computed in the following way. Since both EEG and psychological appraisals have been rated on the basis of a scale of three (good, intermediate, and poor), the per cent average for each criterion has been estimated from the total possible number. Thus, if 10 patients are to be appraised for each of the 11 criteria, according to the amount of good or bad EEG patterns present, the total possible number for each category would be 30 (or 100 per cent if all were "bad" records, but might be only 20 (or 66 per cent if some records were either "ones" or "twos". The results are shown in tables 1 and 2, the statistical validity in table 3.

Figure 6 compares these EEG and psychological ratings for the 70 patients so tested. Many of the differences are significant as shown in tables 1 and 3, although in other categories there are no such positive relationships. For example, "adjustment to environment" is relatively alike in all EEG types. Among these patients, aggression, anxiety and depression are not positively related to any EEG type. But, in the clinical group having "hallucinations", "thought disturbances", "confusional states" and "poor relationships to the examiner", there are relatively few normal "good" EEG frequency patterns and relatively more "poor" patterns. At the other extreme there is a group, whose individuals were found largely among the non-psychotics, which has a high quotient of "situational" element, "lability" and "narcissism", and relatively, a higher incidence of normal frequency patterns. The first group is composed largely of schizophrenics; the last, of individuals who have entered the hospital because of difficulties in environmental adjustment which have to do with psychopathic tendencies. By a psychopath in this paper is meant the individual who has become deviant from the normal because of these qualities of self-interest, narcissism,

TABLE 1.—Correlation of EEG Frequency Pattern with Clinical Data

	EEG:							
	Good		Intermediate		Poor		Total	
	No.	%	No.	%	No.	%	No.	%
Schizophrenic:								
Acute	1	12	3	38	4	50	8	100
Chronic	1	7	10	71	3	22	14	100
All	2	9	13	59	7	32	22	100
Non-psychotic:								
Acute	2	18	2	18	7	64	11	100
Chronic	6	43	7	50	1	7	14	100
All	8	32	9	36	8	32	25	100
EEG:								
Worse	5	50	5	50	0	0	10	100
Better	0	0	6	67	3	33	9	100
Unchanged	5	18	11	39	12	43	28	100

TABLE 2.—Correlation of Psychological Changes with EEG Pattern

	Second Psychological Test:							
	Unchanged		Worse		Improved		Total	
	No.	%	No.	%	No.	%	No.	%
EEG Pattern:								
Good	3	30	3	30	4	30	10	100
Intermediate	4	18	11	50	7	32	22	100
Poor	1	7	3	20	11	73	15	100
Total	8	17	17	36	22	47	47	100
Illness:								
Acute	1	5	0	0	18	95	19	100
Chronic	7	25	17	61	4	14	28	100
Schizophrenic	1	5	11	50	10	45	22	100
Non-psychotic	7	28	6	24	12	48	25	100
Schizophrenic:								
Acute	0	0	0	0	8	100	8	100
Chronic	1	7	11	79	2	14	14	100
Non-psychotic:								
Acute	1	9	0	0	10	91	11	100
Chronic	6	43	6	43	2	14	14	100
EEG:								
Worse	1	10	6	60	3	30	10	100
Better	0	0	3	33	6	67	9	100
Unchanged	7	25	8	29	13	46	28	100

TABLE 3.—Statistical Summary

A. Chi Square Analysis

	Groups	N	X^2
a) Diagnostic category and EEG rating:	Schiz., non-psychot., controls	22, 25, 27	7.803*
	Schiz., non-psychot.	22, 25	4.230*
	Schiz., controls	22, 27	6.667†
	Non-psychot., controls	25, 27	—
b) EEG rating and psychol. change:	"Good", "intermed.", "poor"	10, 22, 15	7.712*
c) Illness and psychol change:	Acute, chronic	19, 28	29.798‖
d) Diagnostic category and psychol. change:	Schiz., non-psychot.	22, 25	5.953†
e) Illness and EEG rating:	Acute, chronic	19, 28	10.058§
f) EEG change and EEG rating:	Worse, better, no change	10, 9, 28	11.305‡
g) EEG change and psychol.	Worse, better, no change	10, 9, 28	6.288

B. 't' Ratio Analysis of Proportions

a) EEG ratings within diagnostic groups:	Poor vs. intermed.	Poor vs. good	Intermed. vs. good
Schiz.	2.11†	1.76	4.40‖
Non-psychot.	—	—	—
Controls	2.48‡	2.22†	—
b) EEG ratings of 70 patients for:			
Hallucinations	—	2.84§	3.42§
Thought disorder	1.34	1.06	2.44†
Confusion	—	1.82	2.02†
Poor contact	1.68	1.20	3.014§
Aggression	1.12	1.02	2.12†
c) Interrelationships of diagnostic groups:	Schiz. vs. non-psychot.	Schiz. vs. controls	Non-psychot. vs. controls
EEG "Good"	1.86	2.72‡	.76
Poor adjustment	3.50§	3.45§	—
Situation	1.70	3.23§	5.65‖
Lability	1.84	2.11†	—
Narcissism	1.84	2.19†	—
Depression	—	2.63‡	2.56‡

* .10 level of confidence.
† .05 level of confidence.
‡ .02 level of confidence.
§ .01 level of confidence.
‖ .001 level of confidence.

and lack of capacity to relate to others together with a tendency to live in the present, not profiting by the past or relating to the future. In previous studies, such individuals have been shown to have a high alpha index and a well-organized EEG pattern (6, 7).

Among the control subjects (fig. 7), the differences between "good" and "poor" EEGs as related to psychological factors are clearer, as would be expected, since these 27 subjects are a more homogeneous group than are the patients. The four controls with poor adjustment had a score of 92 per cent for "poor" EEG design while that of the 11 having "good" EEG patterns was 48 per cent. Anxiety, lability, and aggression here are all related to poor EEGs, and the scoring in all other psychological categories which were applicable to control subjects was higher or "worse" among "poor" records than among "good", in some instances to a significant degree (table 3), thus indicating again, and by a different means, that poor psychological adjustment is in many ways related to poor frequency coordination of the EEG.

Psychotic and non-psychotic patients. A comparison was made between the 22 schizophrenic and the 25 non-psychotic subjects who had, through repeated testing, been appraised at the beginning of their hospital stay and after treatment (fig. 8). As in the data presented in figures 3 and 4, which used different criteria, it is apparent that the more severely disturbed schizophrenic has the less well-designed EEG frequency pattern On the right of figure 8, the data merely indicate the type of psychological adjustment found in the different clinical groups. Probably because the ages of these subjects are relatively young, signs indicating aggression were very frequently found in psychological test patterns; unexpectedly so among the schizophrenics. Anxiety also appeared uniformly high, but depression was definitely less among controls than patients. Situational precipitating factors, lability and narcissistic tendencies were always significantly greater among non-psychotic subjects, this being the group which contained the psychopaths and the disorders of behavior. The relationship of "good" to "poor" EEGs among the three clinical groups is shown on the left of this same figure and has the expected differences.

These data, then, confirm those presented earlier in the article with respect to correlation of EEG frequency pattern and personality structure. They suggest, in addition, that severity of disturbance and possibly schizophrenia are related to more severe EEG disturbance.

Acute and chronic disturbances. When EEG type was compared with clinical and psychological facts relating to acuteness or chronicity of psychological disturbance (table 1), it was found that a stronger, positive correlation existed here. It should be noted that an acute disturbance was one in which the subject, profoundly and immediately disturbed on admission, had evidence in his history of a rather sudden and malignant disorder. This was not always the same thing as the "*situational*" factor recorded elsewhere. There were many instances of immediate situations which merely triggered a chronic process at a relatively slight and superficial level, whereas the so-called "acute" disturbances were those in which the immediate condition of the patient on admission was one of great and precipitate severity, with extreme symptoms of overactivity, verbal volubility and at times violence.

In table 1 it will be seen that the number of subjects is so slight that statistically significant data are unobtainable. However, of the 19 acutely disturbed patients 11 (or 57 per cent) had poor EEGs and only three good records, but of the 28 chronic cases only four had poor records and seven good. In this same table the data are presented in relation to EEG change at second examination. By this form of over-all inspection of the graphs 28 remained unchanged although, by the method utilized in figures 3 and 4 analyzing details of the graphs, more frequency changes were apparent.

Changes in psychological attributes during hospital stay as determined by test material (table 2) were more clearly defined and appeared in about half of the 47 patients. Here again the schizophrenic and the acute cases have different total patterns from the non-psychotic and the chronic. Thus, 95 per cent of the 19 acute cases but only 14 per cent of the chronic cases showed psychological improvement. In contrast 61 per cent of the chronic cases but none of the acute cases became worse. In this table the relationships of change in psychological status and EEG pattern are significant (table 3). For unchanged EEGs occur in seven of the eight with unchanged psychological tests, and there is some preponderance of "worse" and "better" EEGs in relation to similar direction of change in psychological test.

Final conclusion from these data then indicates that it is the relative intensity of the immediate psychological disturbance and its acuteness which are identified with the most severely disorganized EEG frequency patterns.

DISCUSSION

The data assembled above are here presented as suggestive of factors relating the functional patterning of the cerebral cortex to that of personality structure. They are in agreement with and supplemental to previous studies made by a great number of observers over a period of about 30 years. For these reasons the material is here presented although it is recognized that many of its data are not entirely clear-cut. It is to be hoped that a larger series, subsequently superimposed on the present material, will reinforce its indications.

It is inconceivable that any more complete and exact relationship than those previously suggested will ever be found to exist between single psychological factors and single EEG entities, for the assembled complexes of personality under observation are too variable and too manifold. Nevertheless, it seems to be true today, as our knowledge of the brain becomes more particular, that we are becoming capable of more accurate and immediate diagnosis and, hence, treatment.

It appears from present and from previous data that a spectrum of EEG frequency patterns can now be established, at one end of which lies the completely organized and synchronous record of high alpha index and little activity elsewhere (fig. 1). In the unrelaxed state of this subject, the record still is synchronous and coordinate, with a rhythmicity of frequencies throughout recording areas. At the other end of the spectrum lies the totally dys-coordinate EEG having a high incidence of many frequencies rather than a few; a total energy or voltage which is relatively high; an increased capacity for variability, as shown by standard deviations; and an inter-areal cortical dys-coordination which may be very marked.

It now appears that into this spectrum of EEG frequencies individual organization of psychological and clinical entities may be inserted with some confidence that the personality patterns are positively and significantly related to the EEG frequency patterns. At least at the two extremes personality differentiation can now be supplemented and confirmed by EEG patterning.

In the present study, as in the past, the high alpha index, which is usually synonymous with a well-organized frequency pattern such as is shown in figure 1, is related psychologically to a subject having qualities more or less intensely associated with psychopathic personality. Such a pattern appears among the young controls of this series and among the non-psychotics. These are the individuals who have minimal worries and anxieties and who, as described above, relate expressly to their immediate environment, not to their past or their future. They may be psychopaths, as shown by data obtained from prison and mental hospital populations (7), or they may as "successful" psychopaths be a necessary and interesting part of the normal populations. This is suggested by the work of Walter (9) and by that of Williams (10). Recently a report from the laboratory of Gastaut (2) emphasizes this. In a study of the EEG and psychological characteristics of several hundred young individuals, army, air force, and civilian, Gastaut's workers have found the highest incidence of alpha activity among cadet fighter pilots. A similar high incidence of alpha activity appeared in the air-force pilots of Williams' earlier study (10). It is then obvious that this type of individual who becomes a successful pilot must have many characteristics in common with the psychopath in that he is acutely related to the immediate present and has minimal regard for the meaning of the past and future. He is notably also one who has small and transient affective relationships to others.

At the opposite end of the EEG frequency spectrum from that occupied by the well-coordinated and predominantly alpha pattern lies the dys-coordinate and mixed pattern such as is typified in figure 2. There are many intermediate levels of value. It now appears that the schizophrenic personality is significantly related to this second type of cortical activity, and many psychological qualities predominating among the schizophrenics appeared also among individuals from other groups associated with this end of the EEG spectrum. In many respects this psychological pattern may be placed at the opposite extreme from that of the psychopath or of his normal equivalent. For the schizophrenic is less immediately and accurately related to his environment; his perception is often altered and, at times, even his state of consciousness. His past looms enormously in relation to his present and even more so to his future. His reactions to others may be extreme as well as bizarre.

Since there is now a reticular activating system which has been shown in the brain stem to act in a reverberating manner to and from the cortex and since this has been shown to relate to consciousness, it is easy to formulate a mechanism whereby the differences between these types of patient relate to the frequency formulae of their EEGs. On the one hand, in the individual directly and immediately related to his environment, input stimuli are selectively directed via the mesial lemniscus and other pathways, and the cortex reacts relatively simply and directly to such input. The basic EEG pattern then remains relatively stable and uniform. But at the other extreme, in which an inherently unstable cortical reaction pattern is maintained, input is greatly modified and amplified by modulations via reverberations within the nervous system. The resultant disorganized frequency pattern appears to fluctuate in its intensity in relation to the intensity of psychological disorganization and to its acuteness. Since the so-called tranquilizing drugs are thought to work at the level of the reticular substance, the central grey and all the cerebral systems related to them are of the oldest phylogenetic structure and are implicitly organized about the emotions and about autonomic function, also reinforcing any theory which requires the reticular system to play a part in functional psychopathology.

Finally, the longitudinal study of this small series of 47 patients and 27 control subjects suggests that there are changes in frequency pattern organization which are related to severity of psychological deviation at least in those cases which are severely and acutely disturbed. This is more obvious among the schizophrenic group and those non-psychotics who have unstable EEG patterns than among those which have relatively well-organized EEGs with high alpha index. In the non-psychotic group it is the adolescents with disorders of behavior who demonstrate changes and EEG patterns showing marked dysrhythmia.

Speculations from the above suggestive findings may be manifold. Inheritance of instability of EEG pattern and of personality must play a part in the eventual patterning. But it is apparently also possible from our findings to think that the psychological changes which result from environmental stresses and strains can be mirrored by fluctuations in coordination of the EEG frequency pattern.

CONCLUSIONS

1. Observations of frequency pattern of EEGs and comparison with psychological data in a longitudinal study of patients over a period of several months have confirmed the previously recognized fact that EEG frequency pattern is related to psychological function.

2. Previous observations that such factors as anxiety and aggression can be correlated with type of EEG pattern have been confirmed.

3. A comparison of the extremes of EEG frequency characteristics now shows that these relate, on the one hand, to the pattern of personality exhibited by the severe schizophrenics and, at the other extreme, to that of the psychopath as defined in this paper.

4. The above observations have been shown to fit with the data obtained by others in relation to the normal EEG patterns.

5. The single, most significant correlation between the two categories, EEG and psychological, lies in the differentiation between individuals who are acutely disturbed and those with chronic and less violent disturbances. The former show the most extreme disturbances of coordination among EEG frequency patterns on first examination and with psychological recovery exhibit frequency pattern changes. The chronically ill, on the other hand, maintain a steadier frequency pattern and with somewhat less deviation from the normal as indicated by the controls of this series.

6. It can therefore be postulated that overall EEG pattern can be altered in such a way as to deviate from normal frequency relationships by the stresses of situations. It may be assumed from the data that this alteration is to some extent reversible. It is also related to basic and inherent EEG pattern and to the original stability of its organization.

Our grateful thanks are due to Dr. William P. Fister, in whose laboratory at the Provincial Mental Hospital most of these EEG recordings were made. The friendly cooperation furnished by Dr. Fister and his staff over a four-year period was never altered at any point during this time.

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CHEMICAL CONSTITUENTS OF BRAIN AS AFFECTED BY INSULIN HYPOGLYCEMIA, CONVULSIONS AND FEVER[1]

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The work reported in this paper is a part of two larger studies: one, the effects of a wide variety of stress conditions upon the constituents of the brain; the other, the effects of the same stress upon the permeability of the blood-brain barrier. Here we are reporting only upon insulin hypoglycemia, picrotoxin convulsions and fever.

Insulin hypoglycemia was studied not only because of its interest in psychiatric treatment but also because it deprives the brain of blood glucose as a source of energy and forces the utilization of other substrates. Other studies of the effects of insulin hypoglycemia have been reported by Yannet (21), Leibert and Heilbrunn (15), Dawson (6), and Carvioto *et al.* (5). Fever is of interest because of its early use as a treatment for luetic psychosis. Hyperpyrexia also may increase brain metabolism and affect the permeability of the blood-brain barrier. Hartman (8) has discussed the irreversible brain lesions that result from high fever. Picrotoxin was chosen as the prototype of a convulsant since with the administration of this drug convulsive seizures occur repeatedly for a relatively long time. The distribution of minerals in convulsions was studied by Colfer (3).

Three substances have been studied to date: glutamic acid because of current interest in its role in aging and other psychiatric problems and also because it is an active metabolite and is thought to exist in dynamic equilibrium with many other substances in the brain; and sodium and potassium which are of great importance in the conduction and transmission of the nervous impulse.

METHODS

The procedures used for these studies were kept uniform in order that the data obtained over a period of years might be directly comparable.

The experimental design reported here consisted of 5 main groups of rabbits. Sodium and potassium data were obtained in the same animals, while glutamic acid was analyzed in other members of the same main group.

Group	*Treatment*
I. Control	Physiological saline or deionized water
II. Convulsant	Picrotoxin
III. Mild insulin hypoglycemia	Regular insulin
IV. Deep insulin hypoglycemia	Protamine zinc insulin and regular insulin
V. Fever	Typhoid bacillus

The animals in the control groups received physiological saline or deionized water 30 minutes before the brains were removed.

The convulsant group received intravenous injections of picrotoxin under curare and artificial respiration. The dosage was sufficient to produce strong convulsions as confirmed by electroencephalogram (electrodes in limbic and motor areas of the cortex). Brains were removed approximately 30 minutes after the convulsions started and while the animals were still convulsing strongly.

All rabbits used for the work on insulin hypoglycemia were starved at least 24 hours before the experiment. Those animals for the mild insulin hypoglycemia studies received 8–12 units of insulin intramuscularly the day of the experiment. Bloods for glucose determinations were drawn at 60, 90 and 120 minutes after the insulin. Immediately after the 120-minute blood the brain was removed as described below. Blood sugar was determined by the method of Nelson (16).

On the afternoon before the experiment the animals used for the deep insulin hypoglycemia received 10 units of protamine zinc insulin; every hour during the experiment they received 40 units of regular insulin intramuscularly. These rabbits were given nembutal initially in doses sufficient to prevent convulsions. However, by the time the brain was extirpated the nembutal effect had probably worn off completely. The animals were maintained during the entire experiment with artificial respiration. Electrodes were placed as described for the convulsive animals; a heart electrode also was used as an aid to following the cardiovascular changes. The experiment was continued until the heart showed signs of failure as evidenced by dysrhythmia and marked slowing. The animals in deep insulin hypoglycemia showed first a flattening and finally a complete disappearance of the brain waves for an average of more than two hours before the brains were removed. A sample of blood for glucose determination was drawn from a carotid artery at the beginning of the experiment, approximately 9 a.m., again at 1 p.m., and/or just before the brain samples were removed. The time between the first and last bloods ranged from 3 hr., 15 min. to 6 hr., 30 min.

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[1] Read before the Eleventh Annual Convention and Scientific Meeting of Biological Psychiatry, Chicago, Illinois, April 28–29, 1956.

To produce fever in the rabbits 0.1 cc. of a bacterial vaccine of typhoid bacillus (1,000 million/cc.) was injected intravenously approximately four hours before the brain samples were excised. The temperature of the animals was taken rectally at 30-minute intervals during this period of time. The rabbits were allowed free access to food and water. They received nembutal just before the removal of the brain samples.

A uniform procedure for removing the brain was employed. A portion of the skull was removed under local anesthetic exposing the cerebrum. Contamination of the brain by blood was prevented by washing the field with physiological saline solution and aspirating the fluid from the brain surface. The cerebrum and underlying structures cephalad to and including the superior colliculi were excised. Tissues for analysis were taken only from those animals which continued to respire or whose heart continued to beat after this portion of the brain was removed. The brain was rinsed quickly in physiological saline, divested of meninges and external blood vessels, and the hemispheres separated along the superior sagittal sulcus. A segment of each frontal lobe down to and including the head of the caudate nucleus was removed. This sample was called the *caudate nucleus sample*. The remaining portion of each hemisphere was called the *hemisphere sample*. All four parts were immediately frozen with dry ice and ether and stored frozen at minus 18°C. until analyzed. For those brains in which sodium and potassium were to be determined, deionized water replaced physiological saline throughout the procedure.

Acetone-ether powders of brain tissue were analyzed for glutamic acid by the microbiological method as described by Sullivan and Strong (20). Blood glutamate was determined by the technic of Himwich and Petersen (9). For the determination of total glutamic acid, 10 mg. of the fat-free dehydrated tissue were hydrolyzed in 2 ml. 7.8 N NaOH and 3 ml. of H_2O at 15 pounds pressure (121°C.) for four hours. The samples were adjusted to pH 7.0 with acetic acid, filtered and diluted to 25 ml. for assay. Trial assay on casein gave 96 per cent of the calculated total glutamic acid. Only the hemisphere samples were sufficiently large to permit the determination of both free and total glutamic acid. The combined glutamic acid is the difference between the free and the total values. Sodium and potassium were determined with a flame spectrophotometer after the frozen samples had been homogenized in ice water and deproteinized with trichloracetic acid. All blood samples were drawn from the carotid arteries.

RESULTS

In the preparation of the data one of our constant concerns has been that the technic used might allow the contamination of the brain with sufficient blood so that false high values would be found for substances such as sodium which are at a relatively high level in blood. It is difficult to raise the blood level of sodium appreciably without disturbing seriously the electrolyte balance of the animal with the end result of an unphysiologic preparation. Glutamate, however, may easily be raised 100 times over the normal blood level without apparent disturbance of the animal. In two groups of animals used to check the sampling technic the average plasma glutamate values were 1.1 and 158.5 mg.%, respectively, while the average free glutamic acid on a dry fat-free basis in the left caudate nucleus samples was 25.5 and 25.1 gamma/mg. and in the left hemisphere samples 18.5 and 18.6 gamma/mg., respectively. These data suggest that our technic was sufficiently precise to avoid conamination of the brain with a sufficient quantity of blood to influence the data on brain constituents.

Sodium and potassium. Convulsions due to picrotoxin produced a rise in plasma potassium (control 17.7, convulsant 26.7 mg.%) but no significant change in the potassium of the brain samples (table 1). On the other hand, a highly significant increase of sodium in both the left and right caudate samples occurred. In the hemisphere samples there was also a significant elevation in sodium over the level in the control series. Unfortunately sodium was not determined on the blood of this group of animals since the blood drawn was sufficient only for potassium analyses.

The animals maintained in deep insulin hypoglycemia showed marked changes in the sodium and potassium of the brain (table 1). In all areas taken, a highly significant decrease of potassium and an equally significant increase in sodium occurred.

The animals subjected to fever, with an average rise 4°F. over a period of 4 hours, showed no significant change in the distribution of sodium in the brain (table 1). There was a fall of potassium in all four of the brain samples. This fall was significant only in the right caudate sample and the left hemisphere sample. In these animals the blood potassium was at normal level as was also the plasma sodium; 18.6 and 17.7 mg.% for potassium and 348.6 and 348.0 mg.% for sodium in fever and control animals, respectively.

TABLE 1.—EFFECT OF CONVULSIONS, FEVER AND HYPOGLYCEMIA‡

	Potassium	Sodium	Potassium	Sodium
	Left caudate		Right caudate	
Control	329.6 (8)	103.3 (14)	340.4 (8)	105.1 (13)
Convulsions	344.5 (10)	158.4† (8)	356.7 (10)	182.6† (9)
Fever	314.0 (9)	116.3 (9)	315.2* (8)	111.8 (9)
Hypoglycemia deep	276.9† (7)	135.8† (7)	270.9† (7)	139.0† (7)
	Left hemisphere		Right hemisphere	
Control	354.1 (8)	91.6 (16)	350.5 (8)	96.6 (15)
Convulsions	362.3 (10)	114.0† (10)	359.7 (10)	111.5* (10)
Fever	324.0* (10)	93.6 (10)	334.0 (10)	93.6 (10)
Hypoglycemia deep	280.6† (7)	135.8† (7)	273.0† (7)	128.2† (7)

* P = <0.05.
† P = <0.01.
‡ mg.%, fresh tissue.

TABLE 2.—GLUTAMIC ACID IN HEMISHPERE SAMPLES‡

	No.	Free	Combined	Total
Control	20	10.0	65.2	75.2
Hypoglycemia light	42	16.4†	55.1†	71.5
Fever	20	18.5†	46.7†	65.2*

* P = <0.05.
† P = <0.01.
‡ gamma/mg., dry defatted tissue.

Glutamic acid. In the normal control animals the average value for the samples on the dry fat-free brain tissue was approximately 10 gamma/mg. irrespective of the area from which the sample was taken. Data on the effect of picrotoxin convulsions and di-isopropylfluorophosphate convulsions have been reported elsewhere in detail (20). These results do not differ significantly from the control values.

In the animals subjected to fever (average 6°F. for 4 hours) free glutamic acid rose, and the combined form decreased in the hemisphere samples (table 2). In both cases the changes were highly significant as compared with the control values. The decrease in the value for the total glutamic acid was significant only at the 5 per cent level. The free glutamic acid in the caudate nucleus samples was even higher than in the hemispheres, and the difference from the controls was highly significant. The average values for the right and left caudate nucleus samples were 25.4 and 25.8 gamma/mg., respectively.

In rabbits subjected to mild insulin hypoglycemia (table 2) the same changes in free and combined glutamate occurred as in fever but not to as marked an extent although the samples differed significantly (P = <0.01). In these animals the values for the total glutamic acid were substantially the same as in the control group since the change in the free form almost balanced the diminution of the combined. The average free glutamic acid in the left and right caudate nucleus samples was 22.9 and 23.7 gamma/mg., respectively. When these data were compared with the control values, the differences were highly significant. The average blood sugar for the hour preceding the removal of the brain was 44–50 mg.%.

In the deep insulin hypoglycemic group the average blood sugar fell from 51 mg.% to 16 mg.% at the time the second blood was drawn and still averaged 15 mg.% when the brain was removed.

DISCUSSION

Sodium and potassium. Our data on convulsions confirm the well-known fact that sodium increases in nervous tissue with this type of hyperactivity (3). Colfer's work, however, dealt with a redistribution of sodium and potassium between neurones and extracellular fluid. Our samples make no such distinction between cells and extracellular fluid and suggest not a shift in arrangement of the electrolytes but an absolute increase of sodium in the brain. We cannot distinguish whether this increase is in the cell or the surrounding fluid. Colfer and Essex (4) found no change in total amount of sodium or potassium in convulsions due to metrazol or to sound. Physiologically metrazol would be expected to produce less effect on the brain than picrotoxin since the former drug produces a single convulsion. In the present experiments, the changes in potassium were not significant, and potassium in the brains of our animals should be regarded as unchanged. It might be well, however, to point out in this regard that Gell, Polis and Bailey (7) report that acceleration stress caused a marked rise in potassium of rat brain but no change in sodium. However, the preparation studied by those authors was not strictly comparable to ours since our animals were immobilized by the use of curare and prevented from developing even transient anoxia by the use of artificial respiration. Hoagland (12) has shown that swim stress results in an increase in brain potassium, but he reported no data on sodium. The marked elevation in the potassium level of arterial blood during convulsions is probably in accord with that reported by Cicardo (1) and Cicardo and Torino (2). Since the experimental conditions are not described, it is more difficult to explain why Kendall and Essex (13) found no change of potassium in cerebral blood.

The significant fall in brain potassium and the increase in sodium correspond to the data reported by Yannet (21) for cats that showed fatal neurological lesions after insulin hypoglycemia. We, therefore, assume that the animals of our study who were in deep insulin coma suffered irreversible neurological changes.

During fever there appeared to be little real changes in the sodium and potassium of the brain. The fall in potassium, although not significant in any single area, was consistently shown in all four area samples during fever.

Glutamic acid. The data presented here illustrate the dynamic metabolic shifting of glutamic acid. This metabolite is constantly being broken down to aspartic acid or being combined with other substances to form compounds such as glutamine or peptides. In rather mild insulin hypoglycemia of fairly short duration the data show the shift from combined to free glutamic acid with the latter being significantly increased while the former is correspondingly decreased. Such a shift may represent the first step in making free glutamic acid available as a source of energy. Dawson, as well as Cravioto *et al.*, has shown than in insulin hypoglycemia the whole brain of rats contains less free glutamic acid than do the brains of the control animals. Our data do not confirm these results possibly because of differences in the experimental technics used to develop insulin hypoglycemia and the duration of the stress.

During fever the metabolism of the whole body and also probably that of the brain are markedly increased. The data show an increase in free glutamic acid apparently because the combined fraction is being broken down to afford more free glutamic acid for use by the brain. However, in contradistinction to the situation in mild hypoglycemia the total glutamic acid is reduced. It seems reasonable to assume that during periods of high fever even glucose cannot penetrate the brain at a rapid enough rate to maintain metabolism, and the brain turns to some other readily utilizable substance such as glutamic acid to furnish energy. Peiss and his colleagues (17) failed to find an increase of *in vitro* metabolism in the brains of animals with a rise in temperature of

1°C. for the period of one hour. Our animals were subjected to a higher fever over a longer period of time. The dogs with hyperthermia, studied by Hartman (8), were subjected to fever of longer duration and greater intensity than were our animals. No evidence of hemorrhage in the brain, such as Hartman described and no visible evidence of anoxia appeared. The arterial blood in our rabbits was bright red; and mouth, ears, and nose showed no evidence of cyanosis.

The significance of these data requires some discussion. Does the normal brain use glutamic acid as a source of energy, or is its utilization restricted to times when sufficient glucose is not available? In the normal animal it seems well established that the blood-brain barrier is relatively impermeable to glutamic acid (10, 11, 14, 19). The beneficial effects of glutamic acid in insulin hypoglycemia are probably related to its hyperglycemic action rather than to increased rate of penetration of the blood-brain barrier (18). If the brain is forced to break down combined forms of glutamic acid, this represents a sort of self-cannibalism and may lead to irreversible changes in the brain. The data presented here suggest that in deep insulin hypoglycemia severe neurological damage occurs. It is difficult to visualize how such an injured brain can obtain within a short period of time the necessary materials to rebuild its chemical constitution to say nothing of its actual histological structure unless the blood-brain barrier is markedly altered. Data from this laboratory, to be reported elsewhere, indicate that the permeability of the blood-brain barrier at least to glutamic acid is not altered by either mild or deep insulin hypoglycemia. It seems reasonable to postulate that the brain may, when deprived of glucose, use glutamic acid as a substrate but that such utilization should be regarded as pathological and ultimately of serious damage to the organ.

SUMMARY

Picrotoxin convulsions caused an elevation of blood potassium and an increase in sodium in the brain of rabbits. The change of brain sodium is most marked in the caudate nucleus samples. Deep insulin hypoglycemia resulted in a decrease in potassium and an increase in sodium in all brain areas. When the animals were subjected to fever, potassium fell in the brain.

Both free and combined glutamic acid were similarly affected by fever and by mild insulin hypoglycemia. The free glutamate rose, and the combined values fell. These data are interpreted as suggesting that the brain, in the absence of sufficient glucose to maintain metabolism, may use glutamic acid as a substrate. A lack of glucose may arise from a low blood sugar level, as in insulin hypoglycemia, or from breakdown of glucose at a faster rate than it can be supplied from the blood, as may occur in fever.

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THE VALUE OF ELECTROENCEPHALOGRAPHY IN ALCOHOLISM[1]

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Alcoholic patients are ever increasing throughout the nation. The first-admission rate of alcoholics with psychosis to California state hospitals per 100,000 civilian population was 5.9 in 1940 and 7.5 in 1953. This increase in alcoholic brain disease has replaced the former incidence of syphilitic menigoencephalitis, which dropped from 7.5 to 1.5 per 100,000 population in the same period. Furthermore, the rate of admission of alcoholics with or without psychosis now approximates that of schizophrenia. The first-admission rate of schizophrenia in 1953 was 36.2 per 100,000 popularion, compared with 34.3 for alcoholics (fig. 1).

Despite its great importance as a medical and social problem, alcoholism has not received due attention from the general medical profession or psychiatrists. In a recent survey in southern California of psychiatrists' attitudes to alcoholism, Hayman (7) found: "Alcoholics and psychiatrists seem to show a mutual avoidance of each other. Alcoholics usually avoid any type of treatment until their situation becomes desperate," and even if they decide to seek psychiatric help, "few of them seem to be welcome."

This situation, in our opinion, is due to the current orientation of most psychiatrists to alcoholism. As Tiebout (9) pointed out some time ago, psychiatrists as a rule consider alcoholism as a symptom of some underlying condition and do not treat it as a disease in itself. Consequently treatment, in some form of psychotherapy, is directed toward the underlying personality disturbance, and the unsatisfactory results of psychotherapy have usually been explained on the basis of the severity of the underlying personality disturbance.

This concept of alcoholism involves a fallacy. Certainly alcoholic addiction involves an underlying personality disturbance. But once alcoholic addiction is established, there is the added factor of a chronic toxic state due to a constant exposure to alcohol. The character disorder seen in most alcoholics is by then also organically overdetermined, and this condition explains why the character disorder is not more favorably influenced by psychotherapy. For example, judgment defects (a prominent feature in chronic alcoholism) are not psychogenic, but indicate the faulty abstract thinking due to brain damage. This view was suggested both by Goldstein's (5) celebrated studies on the effect of brain damage and by Wechsler (10) in his conclusion: "Controlled studies on the mental effects of chronic alcoholism . . . confirm the loss in mental efficiency observed under experimental conditions and, in general, indicate a progressive, though uneven deterioration in the global functioning ability and personality structure of the chronic alcoholic patient. Outstanding is the impairment of the subject's ability to integrate, particularly at the higher functioning levels."

The organic nature of a given case, however, cannot easily be determined by routine mental examination unless gross intellectual impairments exists. The psychological test battery may point to the presence of an early organic impairment; while medical complications like metabolic changes due to deficiency factors, liver disease, etc. indicate organic pathology. But the organic residual is often overlooked after the acute brain syndrome, the immediate cause for medical care, hasbeen sympatomatically treated. What seems to stand out in most cases after the emergency treatment is the character disorder which tends to mislead the physician about its true nature.

For the past three years we have studied the electroencephalograms of alcoholics, most of whom were hospitalized with some manifestation of the acute brain syndrome. Follow-up

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Read at meeting of Society of Biological Psychiatry, Chicago, Illinois, April 28, 1956.

Presented at the Scientific Exhibit of the American Medical Association, 1956, Chicago, Illinois, under the title "Alcoholic Brain Disease".

Year	Alcoholism with Psychosis	Alcoholism without Psychosis	Total	Syphilitic Meningoencephalitis	Schizophrenia
1940	5.9	24.5	30.4	7.5	20.6
1945	6.0	7.9	13.9	6.7	23.0
1950	7.0	25.4	32.4	2.5	28.5
1953	7.5	26.8	34.3	1.5	36.2

FIG. 1. Extent of chronic alcoholism in California State Hospitals
Alcoholic brain disease has replaced the former incidence of neurosyphilis
Comparison of first admissions of alcoholism with those of syphilitic meningoencephalitis and schizophrenia, 1940–1953
From The California Department Of Mental Hygiene—Dr. Walter Rapaport, Director.

EEG's were taken in many cases. We noted that in some cases the abnormal EEG's improved rapidly, whereas in others they did not return to normal after the acute episode was over. This led to our hypothesis that the EEG may indicate the degree of brain damage in chronic alcoholism. That is, the abnormal EEG which does not improve after treatment of the acute brain syndrome may suggest the presence of a chronic brain syndrome. It provides objective evidence of the beginning phase of the chronic brain syndrome where before only the character disorder seemed apparent.

In the past a number of papers have been published on the subject of the EEG associated with alcoholism. Some concern the effects of alcohol on the EEG, e.g., Davis and Gibbs (4); others deal with the incidence of abnormal EEG's in chronic alcoholics (2, 6). So far none has reported studies on the diagnostic and prognostic importance of the time relationship between the EEG's in the individual case.

Our study, based upon 95 cases, comprises 79 private patients in a general hospital and 16 state hospital patients. In the group of patients admitted to a general hospital, the first EEG was taken either during the acute brain syndrome or immediately thereafter. Repeat EEG's were made in 35 of the 79 general hospital cases and in 12 of the state hospital cases. In 24 cases the second EEG was made within two weeks; in 14 cases within a year; and in 9 cases after more than a year. In 10 of the 47 cases, a series of EEG's was taken. Alcoholism is frequently combined with barbiturism. We have excluded from our present study alcoholics taking barbiturates at the time of admission.

Method of EEG. All EEG's were recorded on an 8-channel Medcraft electroencephalograph. Ten solder disc electrodes were symmetrically applied to the scalp in the right and left frontal, parietal, occipital and temporal areas. In some instances, extra electrodes were applied over the precentral area. Both scalp to scalp and scalp to ear recordings were taken. When possible, asleep and awake records were obtained.

The 95 cases were classified into four groups as follows: The group of alcoholic addiction with acute intoxication showed no evidence of residual pathology after the acute episode was over. The second group included delirium tremens with or without convulsions and those cases in which a brief period of acute hallucination was seen. The third group of chronic alcoholic deterioration showed marked intellectual impairment with character changes after the initial clinical picture of acute brain syndrome was over. The fourth group, Korsakoff's psychosis, included mostly state hospital[2] patients with one exception (a private patient with combined Korsakoff's and Wernicke's disease). A fifth group consists of all alcoholic convulsive cases seen in the above four groups.

The results of the EEG findings, with the distribution of normal and abnormal EEG's are shown in figure 2; the incidence of abnormal EEG's in figure 3; and the comparison between the first and second EEG's in figure 4.

Summary of EEG findings. 1. The majority of all cases, 77.4 per cent, show abnormal EEG's. Those EEG's within normal range fall in the class of alcoholic addiction with acute intoxication or delirium tremens (fig. 2). This substantiates the previous study of Greenblatt (6) and others.

2. The most frequent abnormal EEG in chronic alcoholism is fast activity to more or less degree (fig. 3). This fast activity appears most clearly in the frontal and parietal areas.

3. A great percentage of the fast activity which accompanies the acute brain syndrome

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[2] We are indebted to Napa State Hospital, Imola, California, Dr. Theo K. Miller, superintendent, for furnishing these cases.

First Record of Repeat and Non-repeat Groups Combined	I Alcoholic Addiction with Acute Intoxication	II Delirium Tremens	III Chronic Alcoholic Deterioration	IV Korsakoff's Psychosis	Total	V Convulsive Cases Seen in Four Other Groups
Normal EEG	16 (35.5%)	5 (25%)	0	0	21 (22.6%)	1 (7.2%)
Abnormal EEG	29 (64.5%)	15 (75%)	12 (100%)	16 (100%)	72 (77.4%)	13 (92.8%)
Total	45	20	12	16	93	14

FIG. 2. Distribution of normal and abnormal EEG's

(acute intoxication, acute hallucinosis, delirium tremens) disappears with the treatment, and improvement coincides with restoration of normal activity (alpha). (See the columns of alcoholic addiction with acute intoxication and delirium tremens in figure 4.)

4. Persistent fast activity, slow activity or spike discharges are more frequent in chronic alcoholic deterioration, Korsakoff's psychosis and those cases with convulsions. Particularly slow activity is more prevalent in Korsakoff's psychosis and chronic alcoholic deterioration than in other forms.

Implications of findings. We can infer from the summary that abnormal EEG's which do not clear up after the acute brain syndrome is over point to some residual organic pathology, that is, the chronic brain syndrome (see cases 4, 6). This also applies to those cases in the category of alcoholic addiction with acute intoxication or delirium tremens which showed persistent abnormal EEG's, as in case 3. Because they did not show overt clinical symptoms of the chronic brain syndrome, they were not diagnosed as such. Very likely some of these patients might have revealed intellectual impairment and character changes on careful examination. The theory that persistent abnormal EEG's indicate the presence of organic brain pathology does not necessarily mean that all organic brain pathology is accompanied by abnormal EEG's. On the contrary, in some cases of Korsakoff's psychosis, the abnormal EEG improves to normal despite the remaining organic pathology (see case 8). It can therefore be said that in cases of acute brain syndrome the persistent presence of abnormal EEG's indicates early chronic brain syndrome.

The following cases illustrate EEG findings in the various categories of alcoholic brain disease.

First Record of Repeat and Non-repeat Groups Combined	No.	Beta	Theta	Delta	Spikes
Alcoholic addiction with					
Acute intoxication	45	27	5	1	4
Delirium tremens	20	15	4	0	5
Chronic alcoholic deterioration	12	10	3	1	2
Korsakoff's psychosis	16	12	13	2	2
Total	93	64	25	4	13

FIG. 3. Incidence of abnormal EEG's

Case 1: Alcoholic addiction with acute intoxication. A man of 47 had gone on alcoholic sprees for the past 16 years. On admission he was inebriated, had a staggering gait and slurred speech, but was otherwise pleasant and cooperative. The EEG recording taken the next day showed mild fast activity, which had disappeared by the second recording, 11 days later. In this period the routine treatment consisted of intravenous glucose, vitamins, insulin and high caloric diet; and the patient's general condition improved greatly.

Case 2: Alcoholic addiction with acute hallucinosis. A man aged 48, with a history of excessive, dependent alcoholism for the last 15 years, who had had two convulsions while on a binge, was hospitalized. His delirium, accompanied with auditory and visual hallucinations and bizarre delusional ideas, cleared after two days' treatment. The EEG recording taken at this time revealed very mild fast activity; the second, repeated after 10 days, showed improved alpha with no fast activity. The patient was in good condition at his discharge after 13 days in the hospital.

Case 3: Delirium tremens with character changes. A woman aged 48 had a history of excessive dependent drinking for the past four years. Her drinking was accompanied by irritability, depression, irrational talk and a paranoid reaction against her husband. In one spell she became extremely agitated and unreason-

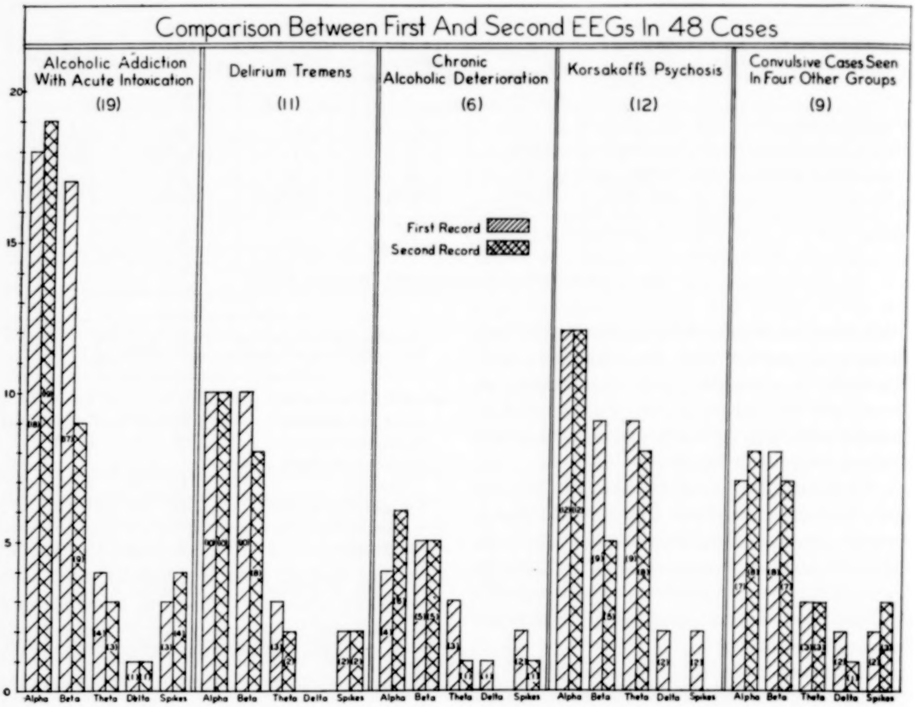

FIG. 4. This figure illustrates the number of cases showing normal or abnormal activity in the two EEG's, but does not take into consideration either decreased or increased activity.

able, had three convulsions in an hour, and was then hospitalized. She had another convulsion shortly after admission, and was delirious, restless and incontinent. The delirium cleared in three days, and the EEG taken then showed severe fast activity; the next two recordings, taken 5 and again 14 days after the first, showed moderate fast activity and mild fast activity, respectively, and thus coincided with the patient's marked improvement under treatment.

Case 4: Chronic alcoholic deterioration with acute intoxication. A 46-year-old woman, a long-time chronic alcoholic, appeared very tremulous and restless upon admission. Physical and mental examination revealed an enlarged liver, severe polyneuritis, defective memory for recent events, euphoric mood and lack of judgment. Yet she was well oriented in all three spheres. Her general condition improved during her hospital course; but the EEG taken 12 days after admission and another taken 12 days later both had the same persistent severe fast activity.

Case 5: Delirium tremens with convulsions. A man aged 50 had begun to drink heavily after his son's death a few years before. At his first hospitalization for alcoholism, delirium tremens developed and was followed by two convulsions. An EEG recording taken on the day prior to the first convulsion revealed slow activity with superimposed fast activity and minimal spike discharges. The second EEG, taken two weeks later, showed essentially the same findings except for a little increased fast activity. The third and fourth EEG's, taken a month and two months after the first, still showed abnormally slow activity but with decreased fast activity and less seizure activity. An acute alcoholic bout necessitated his second hospitalization 1½ years later. His fifth EEG recording, taken at this time, showed much improvement, with only very mild fast activity; but the sixth, taken a month and a half later, again showed generalized slow activity but without spikes or fast activity. The patient was then put on disulfiram and was able to abstain completely. The seventh EEG, taken a few months later, showed a normal pattern.

Case 6: Chronic alcoholic deterioration with acute intoxication. A woman aged 49 had drunk excessively for many years and had had violent episodes, with extreme hostility toward her family. At times grand mal seizures developed during her drinking. During her first hospitalization she completely denied any problems and blamed her family for all her difficulties. Of the three EEG's taken during her three weeks' stay, the first showed severe fast activity and some slow activity; the second and third, moderate fast activity with recovered alpha, but no slow activity.

A fourth EEG, taken a month after her discharge, showed an increased fast activity.

On her second hospitalization, two years later, she was very demonstrative and euphoric, but oriented. A grand mal seizure on the fifth day was followed by a 2-day delirium. An EEG, fifth in the series, taken just before the delirious episode, showed severe fast activity and some slow activity; while the sixth, taken 18 days later, showed some improvement with less fast activity, no slow activity and recovered alpha.

Psychological testing during the second period of hospitalization showed a definite organic impairment.

Case 7: Korsakoff's psychosis. A state hospital patient, a man of 55, with chronic Korsakoff's psychosis, had three EEG's taken at intervals of two months and nine months. All three showed slow activity without other abnormalities.

Case 8: Korsakoff's psychosis. Another state hospital patient, a man of 46, had Korsakoff's psychosis. Two EEG's were taken a year apart. The first one showed fast activity and spike discharges, while the second was much improved, with almost no abnormalities.

COMMENT

We have studied the EEG's of nearly 100 alcoholics and correlated the EEG findings with the clinical course or type of alcoholism by follow-up studies. The results indicate that transient abnormal EEG's accompany the acute brain syndrome, and persistent abnormal EEG's the chronic brain syndrome. This finding is somewhat comparable to our previous EEG study (1) in general paresis, which showed that clinical remissions after treatment correlated with recovery of normal EEG's; whereas failures continued to show abnormal EEG's.

Such correlation of EEG patterns with the clinical course has great significance for diagnosis and prognosis of alcoholics because early organic changes in a given case can be spotted by the persistence of abnormal EEG's, even though only the character disorder is apparent. The customary psychiatric practice is to treat the character disorder as the sole underlying personality problem in alcoholics. We believe the problem is usually dual: 1) the underlying personality disorder, and 2) the character changes due to the brain damage. This condition accounts in great part for failure of insight psychotherapy with alcoholics. They must be treated in a restrained invironment with strong emotional support and must abstain completely from drinking. The dual aspect of causation also accounts for the success of Alcoholics Anonymous with alcoholics.

The exact organic pathology in these cases with a character disorder is not clear. In our opinion it is mainly a cortical atrophy, involving particularly the frontal lobes. Recently Dr. Skillicorn (8) described his necropsy studies of cases of Korsakoff's psychosis; the main pathology appeared in the midbrain and not in the cortex. But Courville (3), who found cortical atrophy in a large number of autopsies of alcoholics, states: "One of the more common noteworthy effects of repeated alcoholic episodes or of chronic alcoholism from constant excessive drinking is a progressive atrophy of the cortex of the frontal lobes. This change affects specifically the convolutions of the dorsolateral surface of this lobe. This relation to chronic alcoholism seems to be one resulting from the toxic effects of ethanol rather than malnutrition (avitaminosis). In the experience of the present writer, it is the most common cause of cerebral cortical atrophy in the fifth and sixth decades of life. It may appear as early as the first few years of the fourth decade, particularly in individuals who have presented signs of a psychotic trend."

In view of these facts we have classified two principal categories of advanced chronic alcoholism: one with midbrain pathology due mainly to avitaminosis, the other with cortical pathology due to the toxic effect of alcohol. The former, consisting of two groups, Korsakoff's psychosis and Wernicke's syndrome, can rather easily be diagnosed as an organic psychosis because of the severe symptoms. The latter class tends to pass as a character disorder because of the subtle organic symptoms. Psychological testing may reveal the impairment of intellectual function in the latter group. But careful EEG follow-up studies should be used to indicate the presence of organic pathology and may be even more accurate and objective because of the comparisons possible in a series of recordings.

SUMMARY

1. Our study on the EEG's of 95 alcoholics shows that the abnormal EEG's which accompany the acute alcoholic brain syndrome tend to improve to normal; whereas those which accompany the chronic brain syndrome tend to persist.

2. These findings indicate that the so-called character disorder of most chronic alcoholics is not the sole underlying personality disturbance, but is organically overdetermined, probably due to a cortical atrophy of the frontal lobes.

3. A new orientation towards alcoholism is emphasized. Alcoholics should be treated as victims of alcoholic brain disease. They should primarily be given strong emotional support, without efforts at insight therapy. All measures should also be taken to have them abstain from drinking in order to prevent further organic deterioration.

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STUDIES ON HALLUCINOGENIC SNUFFS

M. S. FISH AND E. C. HORNING

HISTORICAL BACKGROUND

An interesting custom observed by the discoverers of the New World was the practice by the natives of inhaling a peculiar type of snuff. Ramon Pane, who accompanied Columbus on his second voyage in 1496, wrote of this custom, saying: "This powder they draw up through the nose, and it intoxicates them to such an extent that when they are under its influence they know not what they do" (7). In Hispaniola, where this custom was first observed, the snuff and the ceremony of taking the snuff were called *cohoba*. When under the influence of the snuff, the necromancers, or priests, were supposed to be able to communicate with unseen powers and make prophecies. Medicine men were better able to perform their diagnoses and treatments if they had first taken *cohoba* (8).

It was later found by other explorers and historians that the practice was widespread through northern South America. The German naturalist, Alexander von Humboldt, observed it among the Otomac Indians on the Orinoco River in Venezuela. He described the preparation of the snuff and the method used for inhalation (5). This description closely parallels those made by Richard Spruce, a botanist, and others. In general, seeds of a particular tree were ground, with or without admixture of lime. Some observers say that this mixture was allowed to ferment. A paste was made which was allowed to harden in front of a fire. From this were obtained small, hard cakes which were stored in containers made from snail shells. Before use, the cakes were ground with a type of mortar and pestle. A bifurcated tube (fig. 1), made from the bones of a bird, was employed for the actual inhalation. This custom still is followed in various parts of the Antilles and in South America, particularly in the region of the Amazon and its affluents. The snuff is known by several names, depending on the area where it is used: *cohoba*, *huillca*, *yopo*, *paricá*, etc. The effects of the snuff have been variously described as intoxicating, narcotic, or intoxicating followed by a long soothing action. The words, "debauchery" and "temporary madness", have also been employed in describing the effects.

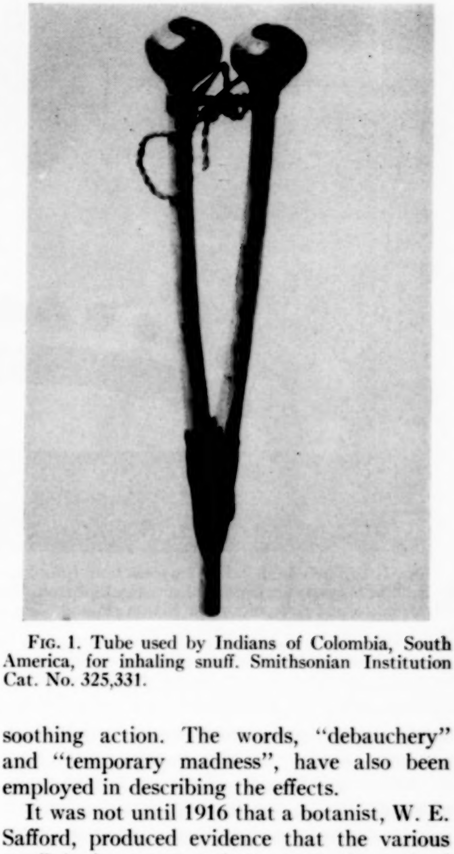


FIG. 1. Tube used by Indians of Colombia, South America, for inhaling snuff. Smithsonian Institution Cat. No. 325,331.

It was not until 1916 that a botanist, W. E. Safford, produced evidence that the various snuffs had a common plant source, the seeds of species of *Piptadenia* (8). This tree is found in the areas where the use of the snuff has been reported.

The Laboratory of Chemistry of Natural Products of the National Heart Institute is currently making a study of these seeds and of snuff samples and has found additional evidence which supports Safford's proposal.

PHYSIOLOGICALLY ACTIVE COMPONENTS

Examination of seeds of *Piptadenia peregrina* (fig. 2) obtained from Puerto Rico showed that the principal alkaloid present was bu-

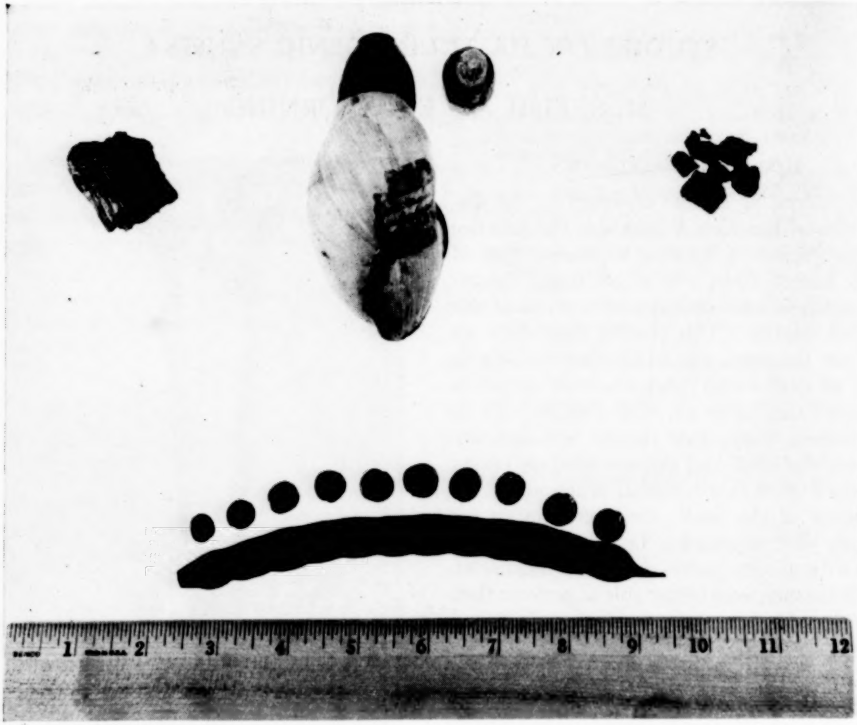


FIG. 2. Top (left to right): *Piptadenia* snuff from Llanos area of Colombia, South America; snail shell employed by Indians for carrying snuff. Collected in 1882 from Mauhes Tribe, Rio Negro, for Brazilian National Exposition; *Piptadenia* snuff collected from Piaroa Indian, Territorio Federal Amazonas, Venezuela. Bottom: *Piptadenia peregrina* seeds and pod, Puerto Rico.

fotenine, an indole compound closely related to serotonin (10). Bufotenine had never before been isolated from a plant source although it has been found in the skin glands of toads and in certain mushrooms. Later on, two samples of snuff (fig. 2), one from Venezuela and one from Colombia, were studied chemically; and, again, bufotenine was found to be present in large quantities. Since the seeds of *Piptadenia* sp. are the only presently known seed source of bufotenine, strong support for the claims of Safford was thus established. Paper chromatographic comparisons of extracts of the snuffs and seeds provided the analytical evidence (fig. 3).

Further chemical study of various seed extracts resulted in the isolation of additional organic bases closely related to bufotenine. One such source, *Piptadenia macrocarpa*, contained five related indole compounds: bufotenine, N,N-dimethyltryptamine, bufotenine oxide, N,N-dimethyltryptamine oxide, and a substance of unknown structure (fig. 3) (2). Structural comparisons (figs. 4 and 5) of these materials with serotonin, the powerful vasoconstrictor which has received much attention recently, and with tryptophan from which all are undoubtedly derived, bring up interesting pharmacological questions: What physiological action, if any, do these compounds have? How do the slight variations in structure affect activity? Work done at the National Heart Institute and elsewhere (6, 9) has indicated that bufotenine, N,N-dimethyltryptamine and serotonin all have grossly similar effects on the cardiovascular system of the dog and cat. No obvious central nervous system effects were observed in these animals at a low dose level. The oxides were much less active than the bases. In the studies of Dr. Edward Evarts of the National Institute of Mental Health (1), it was found that the effects of bufotenine in

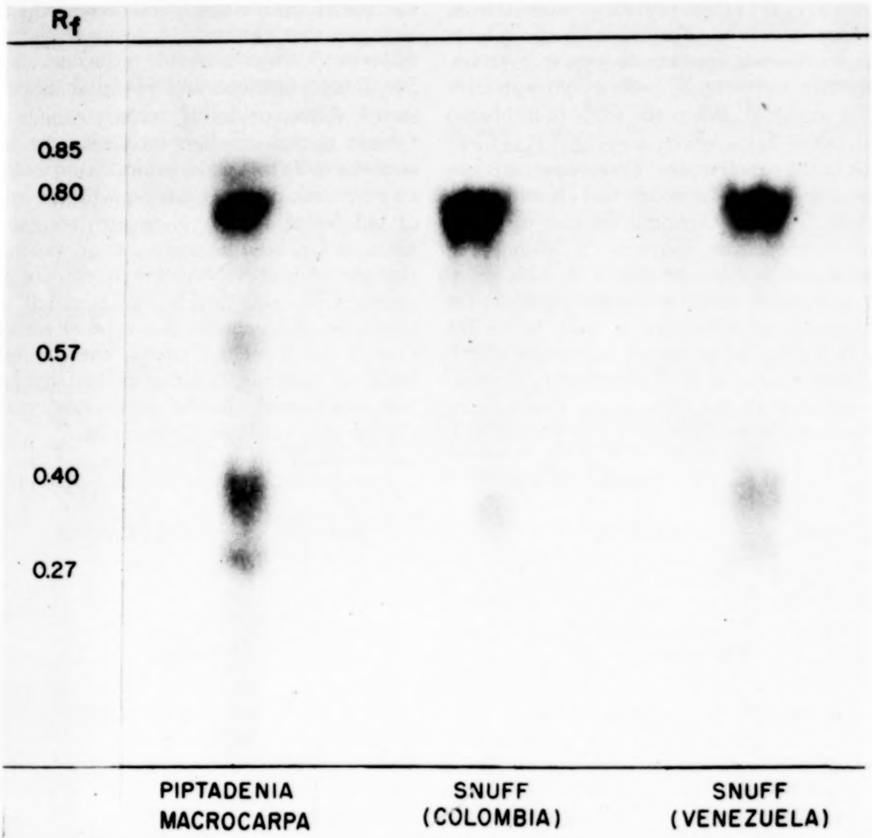


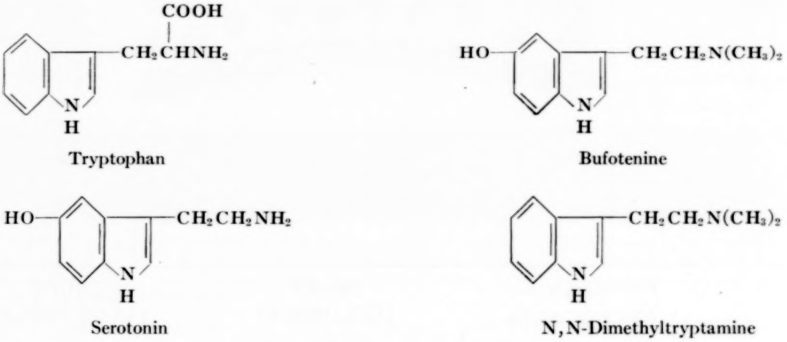
FIG. 3. Paper chromatogram sprayed with Ehrlich's reagent showing indole constituents of (left to right): *Piptadenia macrocarpa* extract; extract of Colombian snuff sample; extract of Venezuelan snuff sample. The intense spots with an R_f of 0.80 are bufotenine.

the monkey were very similar to those of LSD, and that bufotenine and N,N-dimethyltryptamine exhibited similar actions on the synaptic junction of the optic nerve of the cat at approximately equivalent dose levels.

It should be pointed out that pharmacological examination of other fractions of seed extracts has not, as yet, afforded any evidence that physiologically active agents other than the five indole compounds are present. This possibility must not be excluded, however, when one considers the frequent observations pertaining to species differences with respect to physiological activity, along with the fact that animals are not ideal subjects for the study of drug-produced psychoses. For example, in man, LSD is active at a dose level of 0.0003 mg./kg. In the monkey, doses of 1 mg./kg. of LSD and 3 mg./kg. of bufotenine are employed for producing profound behavioral disturbances (1). This difference is 10,000-fold.

CHEMICAL, ENZYMATIC AND METABOLIC STUDIES

A great deal of work on the chemistry of these compounds has been in progress (3). It will be sufficient here to state only that some of these chemical studies were directed toward proof of structure of the indole components of the seeds and that others were directed, as closely as possible, to the duplication of enzymatic conditions. It was found in enzymatic work that some of the products obtained were identical to those previously isolated from chemical reactions. For example, the soluble and microsomal fraction of mouse liver homogenate converts N,N-dimethyltryptamine to its oxide (4). When the oxide is incubated with whole homogenate, some of it is reduced back to the parent amine. These same reactions were also carried out under mild chemical conditions. The mitochondrial fraction of mouse liver homogenate converts N,N-dimethyltryptamine to 3-indoleacetic acid. This is not an unexpected result when one considers the metabolism of bufotenine in man. When Dr. H. D. Fabing administered bufotenine tthe 5-hydroxy analog of N,N-dimethyltryptamine) to convicts at the Ohio State Penitentiary, urine samples were collected and examined. It was found that a small fraction of the bufotenine was excreted unchanged, but the major portion was converted to and excreted as 5-hydroxy-3-indoleacetic acid (fig. 6). Since, as stated above, oxides of tertiary amines are formed by mammalian enzymes, the next step was to learn if these oxides would undergo an enzymatic reaction. Results with the oxides of bufotenine and N,N-dimethyltryptamine have, so far, been negative, but it was found that the oxide of N,N-dimethyltryptophan, an amino acid oxide which was prepared synthetically, did undergo this type of reaction. One of the N-methyl groups was eliminated from the molecule. Another unidentified product was formed. In the latter case, carbon dioxide was lost from the molecule.



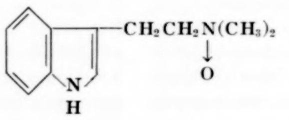
Tryptophan

Bufotenine

Serotonin

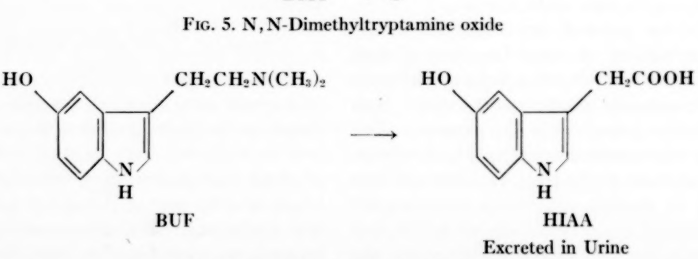
N,N-Dimethyltryptamine

FIG. 4. Structural relationships of various naturally-occurring indoles



DMT → O

FIG. 5. N,N-Dimethyltryptamine oxide



Metabolism of Bufotenine in the human

FIG. 6. Conversion of bufotenine to 5-hydroxy-3-indoleacetic acid in man

The results of these enzymatic experiments have led to the conclusion that a new sequence of tryptophan metabolism should be proposed for plants and possibly for mammalian organisms. The next step will be to learn if any of these compounds plays a vital role in normal or, perhaps, abnormal physiological processes.

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CENTRAL AND PERIPHERAL INDICATIONS OF CONDITIONING, ADAPTATION, ANTICIPATION AND EXTINCTION[1]

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The EEG purports to give information from the surface of the head regarding activity within the brain. The EEG patterns that have thus far been related to identifiable mental states are the low voltage and the slow waves of sleep, the alpha of the inactive waking state, facilitation of alpha in certain conditions of arousal, and "blocking" of the alpha during mental activity. It seems unlikely that this is the limit of information available via EEG regarding cerebral activities relating to mental function. That the phase and amplitude relationships between different brain areas may provide additional information is a possibility which we first explored by drawing ordinates in our records through waves from one part of the head and noting where these cut waves from other areas (5, 6). An instrumental method of wave by wave phase and amplitude comparison of EEGs from different areas has now been developed (7, 8, 9), results from which will be reported with special attention to phase relations. Various automatic devices and methods have been described for phase analysis of the EEG. Hugger (14) presents a statistical method; Walter and Shipton (19) investigate phase using an elaborate cathode ray "toposcopic" display system. Cohn (4) describes a simple method of projection toposcopy; Sonneman and Kennard (18) describe an "interphase analyzer"; Goodwin and Stein (13) have developed a "correlator" providing integration of the amount of in and out-of-phase activity; Rémond and Offner (17) have developed a method of temporally fractionating EEG and comparing corresponding time intervals; Brazier and Casby (2) have used an "autocorrelation" technic for establishing self-consistency of EEG time relationships; and Barlow and Brazier (1) and Dawson (12) have proposed improvements in autocorrelation instrumentation.

Our device involves a "bipolar" comparison of either the positive or negative halves of EEG waves after elimination of the other half by rectification. By thus supplying simultaneous EEG voltages of the same polarity, respectively, to grids I and II, bipolar comparison gives a record in which waves that are equal and in-phase cancel. Waves which are in-phase but unequal indicate the larger. Waves which are out-of-phase by less than 180° show their respective lead or lag by directional diphasic patterns. Waves 180° out-of-phase are additive and approximate a sinusoidal diphasic pattern.

The EEGs here compared are anterior-posteriorly spaced leads on the upper convexity of the head about 3 cm. lateral to the midline roughly designated frontal, motor, parietal, and occipital. These were recorded against a common lead from both ears. Different combinations of areas were compared under various stimulating conditions in different subjects by the six available comparison channels in quest of significant or unique features of relationship. For present analysis the comparison which showed the most pronounced changes among several tried on each subject has been scored second by second and tabulated. Comparison of motor with occipital areas has most frequently been used, but in some individuals this wide anterior-posterior spacing gave a more or less continuous preponderance of out-of-phase or occipital leading regardless of stimulating conditions (fig. 6), and the more closely spaced parietal-occipital comparisons showed greater lability under experimental conditions and was used. Differences in possible significance of these two comparisons are under investigation. It seems likely that there are individual differences in degree of anterior-posterior phase relationship which will repay further study.

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[1] This work was supported in part by a grant from the Illinois Department of Public Welfare Mental Health Fund. Presented before The Society of Biological Psychiatry, April 28–29, 1956.

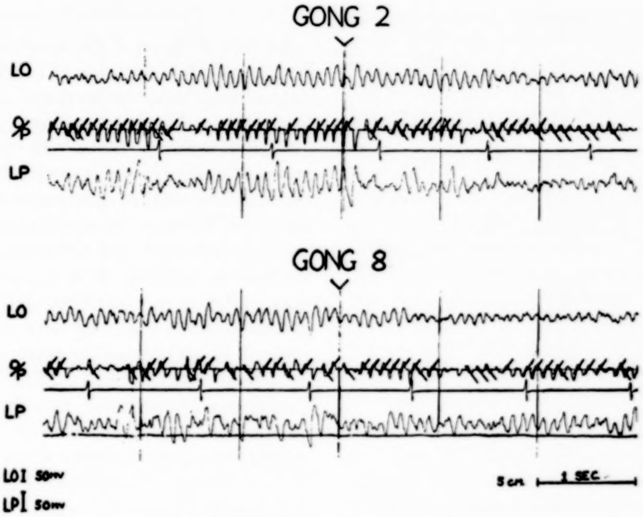

FIG. 1. Instrumental comparison

In an attempt to evaluate the functional significance of phase relations, we shall give results on some of the more readily accessible conditions of cerebral function, namely those indicating adaptation to, anticipation of, and conditioning to repeated stimuli in normal young adult subjects. We shall use regularly repeated gong stimuli at 10-second intervals, and conditioning of a buzzer to the sound of a loud auto horn regularly repeated at 20-second intervals as main conditions. Observations on other forms of unconditioned stimuli such as a loud rap on the door, electric shock, flashing light, and motor activity will also be mentioned. Different phase relations involving anterior leading, occipital leading, in and out-of-phase EEG, along with palmar galvanic response, cardiac and respiratory activity will be illustrated.

To the extent that alpha waves of different areas can be compared by this method they are of necessity not subject to extreme "blocking". Accordingly in noting effects of repeated gong stimuli, we shall disregard the 1st gong, which is most often characterized by excessive blocking and movement artifacts, and use the 2nd, 3rd, and 4th gongs as representative of early stages of stimulation. We shall, furthermore, omit from our count 6 cases who, after eliminating gong one, still gave blocking or what in our comparison records are referred to as "cancellation"[2] effects sufficient appreciably to alter the data on phase. This leaves 14 cases for comparison of phase changes at the beginning and at the end of a series of gongs in which the cancellation effects did not greatly reduce second by second measurements of phase.

INSTRUMENTATION

For this investigation we employed electrically recorded respiration, EKG, heart rate, and palmar galvanic response, both as resistance, by the Féré (bridge) method, and as differential skin potential, by a modified Tarchanoff technic. A 16-channel Offner dynograph supplemented by 10 accessory high gain pen writers provided the basic recording equipment. Six channels of conventional unipolar EEG are recorded in parallel with six comparison channels. In certain instances the amplitudes of some of the EEG channels have been increased or decreased one step, more nearly to match the amplitudes of other channels.

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[2] "Cancellation" in the comparison channels includes both reduction due to equal in-phase activity and that due to "blocking" in compared channels.

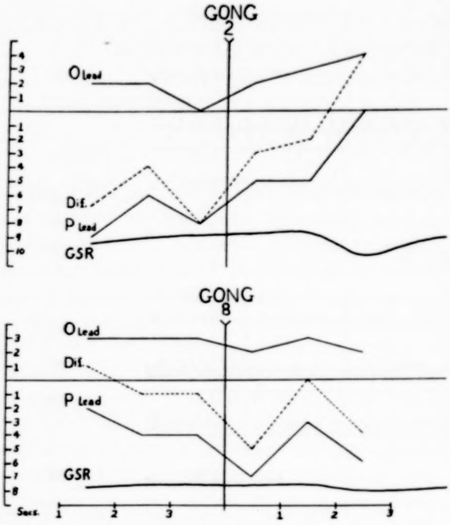

FIG. 2. Effect of repetition

To test the effects of adaptation and anticipation of regularly repeated stimuli, loud gong sounds (banging a brake drum) were presented at 10-second intervals. An example of phase analysis is presented (fig. 1) in a selected sample involving reactions to the 2nd and the 8th gong presentations. It shows motor and parietal area records with the wave-by-wave comparison between them. The present comparison is based upon the fact that when a wave in one compared channel precedes a wave in the other by half a wave length or less, the overlapping compared curves give an unbroken diphasic transition of the comparison base line. We have scored the comparisons by accenting the unbroken diagonals with heavier lines of corresponding slope. Anterior leading in figure 1 is sloped toward the right, and occipital leading toward the left. Combined anterior and posterior leading in the same wave indicates approximation of the 180° out-of-phase relationship and will hereafter be referred to simply as "out-of-phase". Second by second scores of anterior and posterior leading are determined by count and have been graphed in figure 2. To the extent that the various experimental conditions appear to affect anterior and posterior leading differently, these differences may be psychologically or neurophysiologically important.

PHASE RELATIONSHIPS

As seen in figure 2 the incidence of anterior leading tends to decrease as incidence of occipital leading tends to increase, and vice versa. Occipital leading is accordingly plotted in one direction upward above the base line, and anterior leading in the opposite direction below the line. The total or differential effect—or possibly the "balance" or equilibrium between the two—is indicated as a difference by the intermediate dotted line. It is apparent in figure 2 that, after some anticipatory effects, early presentation of the gong here produces an increased incidence of occipital leading and a decreased incidence of parietal leading. The "difference" indicated by the dotted line shows the combined effects. After several repetitions, gong 8 shows a reversal of direction of change. The attendant palmar galvanic response also is greatly reduced with repetition.

Effects of repeated gong stimuli on the 14 individuals with minimal blocking are shown in figure 3. Combined reactions to gongs 2, 3 and 4 are similar to those shown for 2 in figure 2. Development of a preparatory or anticipatory effect seems clearly indicated. The proba-

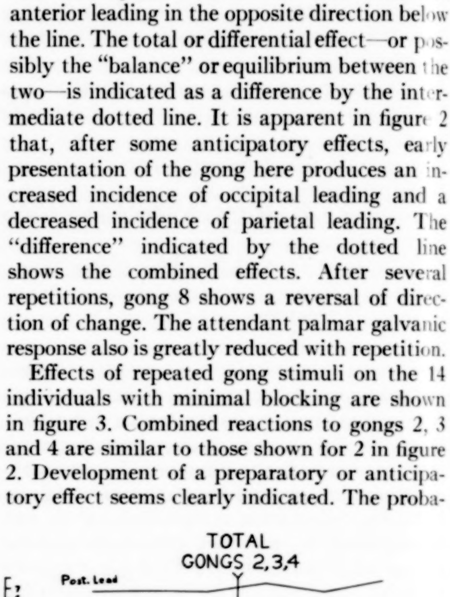

FIG. 3. Mean repetition effect

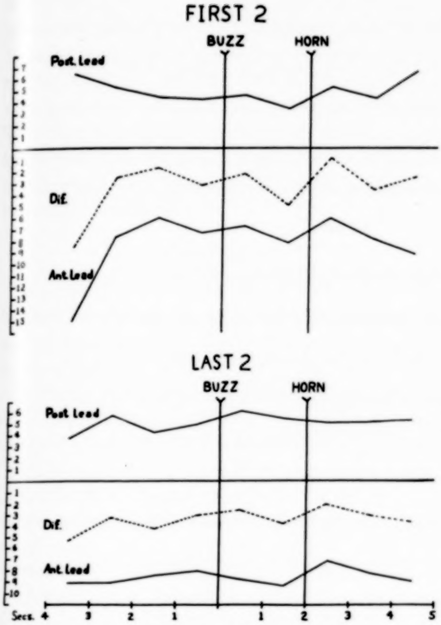

FIG. 4. Effect during conditioning

bility that the response to gongs 2, 3 and 4 would occur by chance in the 20 individuals with and without marked "cancellation" is .02. The probability among these individuals that the reduction in response as compared with the last 3 gongs in a 9 to 12-gong sequence is due to chance is less than .01 (i.e., one in 100) in the case of anterior leading, less than .02 for the difference between anterior and posterior leading, and not reliable in case of occipital leading. Mean galvanic response is greatly reduced with repetition, and the possibility of chance occurrence of such a difference is roughly .001, i.e., less than one in a thousand.

Essentially similar conditions of reaction and adaptation in a conditioning experiment were explored with 20 subjects in whom the sound of a buzzer was conditioned to an "unconditioned" auto horn stimulus. Data for the 10 subjects with least blocking are presented in figure 4. Similar initial reaction, anticipatory, and adaptation effects were obtained for the horns as noted above for the gongs. Galvanic response to the buzzer was eliminated by repetition before presenting the buzzer with the horn. As seen in figure 5 reaction to and anticipation of the buzzer appears to have been built-up before presentation with the horn. Following conditioning, the response to the buzzer appears to indicate an adaptation effect like that for the horns.

PHASE AND RELATIVE DOMINANCE

The diverse and complex patterns of EEG phase relationship involve, of course, the interaction of different areas. Most frequently observed of interactive patterns is one in which the resting-waking activities of motor and occipital areas are much of the time approximately 180° out-of-phase, and shifting phase relationships appear to occur as a result of varying spread of "relative dominance" (10) of anterior versus posterior influence and competition for intermediate areas. Thus, when anterior patterns spread sufficiently to dominate the parietal, motor and parietal areas become in-phase and the parietal becomes out-of-phase with the occipital. On the other hand, when occipital influence is widespread and dominates the parietal, these two are in-phase while the parietal and motor become out-of-phase. Earlier manual graphic analysis

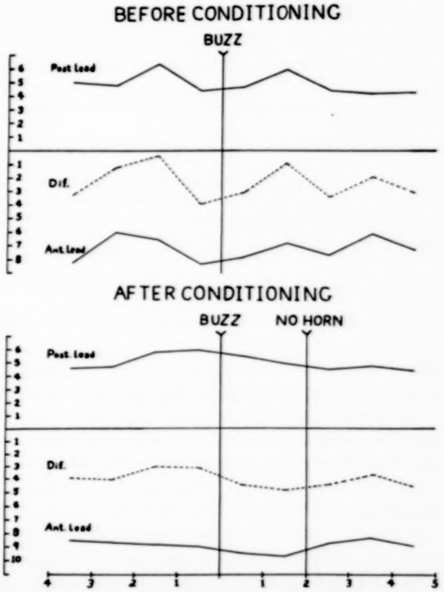

FIG. 5. Effect of conditioning

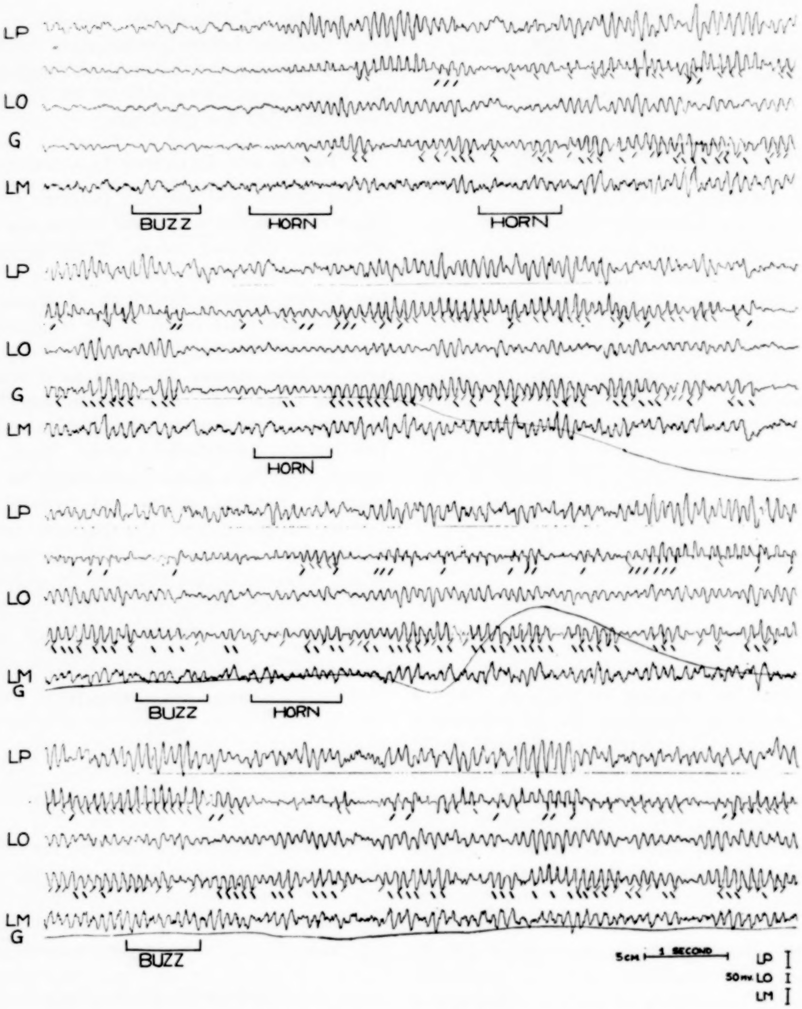

FIG. 6. Arousal and excitation

(10, 11) showed spreading anterior dominance of the EEG extending during bodily reactions in an out-of-phase wave front into the parietal-occipital region. Shifts in phase may also be attributed to the automatic slowing attending increased amplitude, and to the increased frequency attending decrease in amplitude (15). For example, increased motor area voltage with slowing following stimulation may change motor-out-of-phase-with-occipital to motor-leading-occipital. The possibility that out-of-phase anterior-posterior alpha resonance may provide a mechanism of recruitment for alpha amplitude is suggested by the frequent coincidence of out-of-phase with increased over-all amplitude.

Further illustration of relations of anterior and posterior leading to reaction, anticipation and adaptations is provided in the reactions to successive gong stimuli in figure 6. Especially to be noted is the in-phase activity (unscored) immediately after the first horn with subsequent parietal leading occipital (diagonal sloping right) following horns 2 and 3. Increased occipital leading parietal (diagonal sloping left) follows horn 4 attended by a strong diphasic palmar skin potential response. The motor-occipital comparison shows a high incidence of occipital leading with out-of-phase (combined parietal-occipital leading) following each stimulation.

DISCUSSION

Instrumental comparison of EEG phase relations involving the relative lead and lag of waves from anterior compared with posterior head areas has been reported under varying conditions of reaction, anticipation, adaptation and conditioning. Evidence has been presented of cerebral changes other than blocking following stimulation, and, possibly more important, indications of changes in the brain which may occur in anticipation of repeated stimuli and adaptation to or defense against expected stimuli.

Immediately following gong, buzzer and auto horn stimulation, parietal-occipital and motor-occipital comparisons showed decreased tendency for waves from more anterior areas to precede or "lead" those from more posterior areas and an increased tendency toward posterior leading. Although in some cases this tendency in our data may attain to statistical reliability, it is clear that as far as our observations go there are no one-and-one correspondences of phase and function within the frequency range studied and no demonstrated causal relationships. We may not conclude, however, that phase is necessarily functionally unimportant. As often happens positive findings are significant, but negative results are inconclusive.

It is assumed that alpha or other waves which we record and compare represent bursts of rapid thalamo-cortico-thalamic activity in a 10 per second alternating excitability cycle (16) and give rise to dendritic and other potentials in the cortex (3). The alpha or other patterns which we compare are the total smoothed-out contours and over-all envelopes or curves of distribution of this activity. It is conceivable that a barrage of impulses arriving in one area earlier than a similar barrage elsewhere should cause a displacement of the brain wave curve of distribution and give a recordable shift in phase relations. On the other hand, the absence of a displacement of the total curve does not prove the absence of lead or lag in contributory subgroupings. Lesser volleys of leading in one direction or another, though not apparent in the record, may still be functionally effective. Furthermore, it appears that observations on the spread or "relative dominance" of waves of different areas must be combined with those on phase relations in order to reach understanding and a useful application of this technic.

SUMMARY AND CONCLUSION

Results from a new instrumental method of wave-by-wave phase and amplitude comparison of EEGs in different areas have been presented under conditions involving reaction anticipation, adaptation and conditioning. Results show a tendency for more anterior areas to lead more posterior areas during resting-waking conditions and for occipital leading to increase and anterior leading to decrease immediately following stimulation. Both phase and relative amplitude or "dominance" and spread of activity in different areas are involved. It is confirmed that changes in EEG other than "blocking" of alpha activity occur in reaction to stimulation, and in anticipation of expected stimuli.

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PHYSIOLOGICAL DETERMINANTS OF THE DREAM PROCESS

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The dream is generally recognized as a dynamic process having a unique form and a significant content. Apart from its intended purpose for human existence it has proven quite helpful to the clinician doing therapy. There are, however, constantly recurring questions bearing on the crucial points of dream theory which have never been firmly set to rest by psychological considerations alone. These pertain to the adequacy of the postulates of guardianship of sleep as the function of the dream and of wish fulfillment as the motivation of the dream. Further questions arise concerning the hypothesis that the attributes of the primary process (in the Freudian sense) determine the illogical, representational form of the dream and that the content of the dream itself is a disguised end product of the struggle between an unconscious impulse and the surrogate of the ego in the form of the censor.

The most striking characteristic of the dream is its association with the altered state of consciousness occurring during sleep. Although current dream theory appears to take this into account, it does so in a manner which reveals a certain bias in the direction of rendering the dream useful for considerations of the waking state without furthering or clarifying our understanding of the connection of the dream to the time of its occurrence and to the very profound physiological alterations that characterize the sleeping state. As a consequence of the trend in recent years to focus on the psychology and the interpretative value of dreams, many earlier and promising physiological views have remained suspended in mid-air. I wish to develop one such earlier view, namely, one proposed by Pavlov, to see whether or not it can explain the significant facts about dreams and do so in closer accord with the growing body of neurophysiological data on the sleeping state. I am embarking upon this as a clinician in the hope that it may prove fruitful in setting certain realistic limits to our theoretical use and understanding of dreams.

Pavlov made many scattered references to dreams, but nowhere as far as I know did he reveal any great interest in them *per se* or treat them in any systematic fashion. His theory of dreams is intimately connected with his inhibitory theory of sleep and with his concepts of the primary and secondary signalling system. According to Pavlov the primary signalling system mediates those responses based on direct sensory interaction with the environment. In man there is a further elaboration by means of the secondary signalling system enabling the organism to deal with the environment through signals of these sensory impressions in the form of words and language. The following brief passage is selected as representative of his views. Referring to the early stages of sleep he states (11):

> "Then instead of the usually predominant (in the waking state) function of the second signalizing system, there arises the activity of the first system, primarily and more stably as fantasies and day dreaming, but further and more definitely as sleep, dreaming, and drowsiness, freed from the regulating influence of the second system. Hence, the chaotic character of this activity depending chiefly upon the emotional influence of the subcortex."

The essential point made by Pavlov is the connection between the occurrence of dreams and the relative dominance of the primary signalling system during the transitional state between deep sleep and waking. As thus stated, our starting point is little more than an idea, but a most valuable idea arising as it does on the basis of long and fruitful investigatory work on conditioning and insofar as it represents an attempt to relate dreams to concomitant changes of a specific physiological nature.

To develop this idea into a theory of dreams involves its extension in two directions: first, physiologically to explore the interconnections of dreams and sleep, and secondly, psychologically to clarify the relationship of dream consciousness to waking consciousness. The emphasis for the purposes of this presentation will be on the former task since the psychological extension of the theory has been developed in a previous report (12). The main tenets of such a physiological extension, the data upon which they are based and the implications they have for the dream, may be briefly outlined:

1. Dream consciousness is related to the concordant activity of the sleeping individual much as waking consciousness can only be conceived of as consciousness of waking activity. The activity of the individual during sleep takes place at an involuntary level. Aside from the setting of limits under certain conditions, as for example, the ability to awaken at a specified time, the movement through the various phases of sleep and within those phases themselves, is not directly controllable. This statement is both empirically derived and experimentally validated. There is a body of evidence based on electroencephalographic studies (1, 4, 9) pointing up the continual shifting movement towards states of lighter or deeper sleep. The work of Hess (6), Magoun (10) and others has defined with great accuracy the subcortical structures controlling the maintenance of sleep and the arousal reaction. There is further electroencephalographic evidence that dreams tend to occur in the lighter stages of sleep (1, 4, 5). We can, therefore, state that the only significant activity engaged in by the sleeping individual is the activity of being carried in an involuntary fashion through various levels of depth of sleep and that at times these levels are light enough to be accompanied by some manifestations of consciousness. This particular type of activity is reflected subjectively in dreams insofar as they are passively experienced in an over-all sense. They are unwilled and unexpected. They are accompanied by the felt reaction on the part of the dreamer of being an enforced participant in a drama that has come about by forces beyond his control. The sense of participation may occur as the dream develops, but it is a derivative and secondary feature of the experience.

2. The dream, reflecting the involuntary transitional activity described above, becomes a factor in turn influencing that activity. This is based on the hypothesis suggested by Bremer (2) that the cortex participates in its own arousal by means of corticofugal impulses impinging on the ascending reticular activating system. He and other investigators (7) have called attention to the reactivity of the reticular formation to cortical stimulation. The dream appears to be the manifestation of such cortical excitation arising during sleep. As such it may be regarded in a unified manner as one, albeit an important one, among many stimuli impinging upon the reticular formation. The nature and extent of the arousal reaction are determined by the summation of all stimuli on the subcortical centers at any given moment. Seen in this way the dream has meaning as an occurrence analogous to a sensory stimulus. In the waking state, our consciousness is adaptive insofar as there is an integration and elaboration of stimuli at the level of abstraction and conceptualization leading to a discriminatory and planned mode of behavior. In the sleeping state dream consciousness subserves a sensory function and either participates in the process of transforming itself into waking consciousness by its arousal impact on the reticular formation or in its own dissolution if its effect is subliminal with respect to the sleep maintaining activity of the lower centers. This concept has relevance for understanding the appropriateness of the representational character of the dream and in so doing dispensing with the view of the dream as a regressive or more primitive mode of thought. The representational form which mainly involves the use of visual imagery is the only means whereby all the complicated features of waking consciousness can be so organized as to function at a sensational level and produce the unitary response of altering the movement during sleep in one direction or another. It has further relevance to the one-sidedness of the guardianship of sleep theory. In the view presented the dream is an arousal stimulus which may or may not be sufficient to bring about complete cortical activation. This appears to me to be more in accord with empirical observations based on my own experience with dreams as well as those of my patients that partial or complete awakening occurs more often than is generally believed following a dream. Gerard (5) points out that the presence of dreams does not prevent the arousal reaction from proceeding to awakeness. This bi-directional outlook for the dream stands in contrast with the Freudian view that were it not for the dream, a distressing wish would be more apt to cause awaken-

ing. The unfulfilled wish is seen by Freud as initiating the dream, and by means of the dream work there follows the illusory fulfillment of the wish. If instead of this we simply assume that at certain times the stimuli impinging on the activating system are sufficient to initiate cortical arousal, we are then in a position to place primary emphasis on the actual conditions and circumstances in which the dreamer finds himself at the moment and to see the subjective experience of the dream as related to these circumstances. In other words, what has to be reflected out of the individual's past experience at the time of cortical arousal must have relevance to the fact that, first, there has been a disturbance in the form of a movement from one state of sleep to another; second, that this movement is occurring under conditions that are not directly controllable; and third, there are only two possible end points to the movement, namely, complete waking or movement to a maximum depth of sleep. For an aspect of waking experience to be appropriate to the needs of the individual at this time, it must thus have 1) the quality of being disturbing to the individual, 2) a quality of having an involuntary or unmastered component, and 3) the quality of having a meaning derived from past social existence and directed toward future social existence, a meaning which when transformed into concrete sensational terms endows the dream with a certain intensity as a stimulus. Depending on this intensity there may or may not be a return to waking consciousness. Under certain circumstances unfulfilled wishes and longings may meet these criteria, but they do not do so exclusively. In the so-called infantile dream which appears to be so transparently wish-fulfilling, the view here postulated would be first that the frustrated activity derived from waking life is concretely expressed. It then has an arousal impact upon the activating system which is insufficient or subliminal. There follows a return to deep sleep and with it the dissolution of the disturbing presentation. The dreamer, however, experiences only the return to deeper sleep and the elimination of the stimulus. He reflects this movement and the elimination of the stimulus in subjective terms based on his past experiences in the waking state which have on previous occasions resulted in the elimination of such stimuli. He thus dreams of having food, for example, if hunger is the stimulus or of having gone to the bathroom and urinated if the disturbing stimulus has arisen from the bladder. He has simply used his past waking experience to reflect the fact that the stimulus has been rendered inoperative. Linn (8) has developed the interconnection of the dream with the activating system in a somewhat different manner. He suggests that the cortex scans incoming perceptions for their danger potential and signals the activating system accordingly. The dream is seen by him as lowering the arousal potential of certain perceptions. This is in contrast with the view presented here that the translation into dream form takes place only for the purpose of *expressing* the arousal potential of the stimulus in a form that is suitable for evoking a response from the subcortical centers.

3. We have thus far offered a functional explanation for certain characteristics of the dream that appears to be in accord with the growing body of experimental data on the sleeping state. The final proposition which I wish to place before you is that the Pavlovian concept of primary signalling system dominance suggests the nature of the physiological mechanism that brings about the profound alterations in consciousness that characterize the dream.

The concept of the primary signalling system implies in the first place that there is something analogous here to the way in which lower mammals ordinarily function. They are guided by concrete rather than by abstract aspects of reality. Reality impinges on them in an immediate rather than in a time-binding sense. Their activity occurs at a relatively more involuntary level in the sense of their greater dependence upon the immediate demands of their environment. We have already noted that these three features do in fact characterize the dream process. Consciousness assumes a concrete form evoking either a lighter or deeper sleep. The dream reflecting an activity in the present and limited to the present is characterized by a sense of immediacy. Finally, inasmuch as the activity itself is of an involuntary nature, the dreamer finds himself without the sense of freedom that characterizes his waking relationship to his environment. The spatial and temporal distortions and the lack of logic are understandable when one considers that the task of the dreamer is not to reflect his past experience in a communicative sense but to reflect it at a sensational level and only for the purpose of its arousal potential. In other words, what takes place is not the coming together of conflicting streams of impulses out of which a compromise is effected by means of the dream work, but the situation is one in which the conflicting and unmastered aspects of waking activity are simply experienced differently by virtue of being refracted through the concretizing prism of the primary signalling system.

There are indications apart from a consideration of dreams themselves of what may be referred to as a reduction process, whereby the conceptualized relations characteristic of the second signalling system are reduced to the level of sensational stimuli. This term has the negative advantage of avoiding the use of loose and inappropriate terms like release and regression in relation to the dream. Bridger and Gantt (3) have demonstrated this effect occurring in dogs following upon the use of mescaline. They found that under the effects of the drug the dogs responded to the conditional stimulus tone as if it were the unconditional stimulus or the electric shock itself. On the basis of this they suggest

> "that under the inhibitory effects of mescaline and its resulting dissociation, the normal relations between conditional and unconditional stimuli are disturbed and the conditional stimulus begins to have an effect on the animal as if it were the unconditional stimulus—the signal of reality comes to act as if it were reality itself."

They extend this idea to humans as an hypothetical explanation for the psychological symptoms of mescaline intoxication.

> "Mescaline produces an inhibition and cleavage of the normally coordinated three systems of higher nervous activity; that is the unconditional or inborn reflexes and the first and second signalling systems. Furthermore, with this disorganization, just as the primary conditional stimulus comes to act as the more primitive unconditional stimulus, in humans the second signal system of words, ideas and abstractions comes to act as if it were the more primitive, primary conditional reflex system of direct concrete impressions of stimuli. Thus verbal concepts or abstractions of reality come to act like direct impressions of reality itself."

We see then that the use of mescaline elicits the same reduction effect experimentally that occurs spontaneously in the form of dreams or hypnagogic imagery and that is met with pathologically in the various schizophrenic states. The schizophrenic has often been referred to as living out a dream in the waking state. In addition to the literary overtones and psychological possibilities of this formulation, there may have been significant physiological implications as well.

CONCLUSION

The effort has been made to correlate the form and content of dreams with the more recent findings concerning the role of subcortical centers in the control of sleep and with the Pavlovian concept of the relative dominance of the primary over the secondary signalling system. The unique formal characteristics of the dream as well as the dynamic nature of dream content can be adequately explained without recourse to the concept of special psychic forces.

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BIMEDIAL LOBOTOMY: FIVE-YEAR EVALUATION[1, 2]

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Bimedial prefrontal lobotomy was introduced in the treatment of chronic intractable mentally ill patients at the Boston Psychopathic Hospital in 1948. The incidence of untoward side effects such as reduced initiative, flattened emotional responses, and convulsions following the full bilateral procedure suggested the need for limited modified lobotomy which, through selective cutting of brain tissue, might maintain or increase benefit, yet reduce or eliminate deficit.

The "Second Lobotomy Project" of the Boston Psychopathic Hospital was designed to compare the therapeutic effectiveness of three lobotomy procedures, i.e., bimedial, unilateral, and full bilateral lobotomy, in 116 chronic mentally ill patients. Patients were randomly distributed into three groups, each of which differed essentially only in the type of lobotomy procedure employed. The clinical results at *one year*, which are fully presented by Greenblatt and Solomon (1), revealed superiority of the bimedial operation. The same patients have now been re-investigated *five years* after lobotomy to determine which, if any, of the three operative procedures is preferable with respect to long-term clinical results. It was possible to get pertinent follow-up data on each of the original 116 patients.

In substance, the five-year re-investigation confirms the superiority of bimedial over bilateral and unilateral lobotomy and also establishes the fact that, by and large, post-lobotomy gains visible at one year are generally sustained to five years.

Over-all improvement. Table 1 presents the changes in the levels of improvement in each of the patient groups at five years. A "marked" improvement rating was given to those patients who showed dramatic relief of all mental symptoms including disorganization of thought hallucinations, severe anxiety and tension, etc.; these patients generally also showed improved work adjustment whether in the community or in the hospital. "Moderately" improved patients were those who showed considerable gains in most areas. "Significant" improvement included all patients who exhibited either "marked" or "moderate" levels of improvement. "Significant" clinical improvement at five years was observed in 65% of the bimedial patients, compared with 44% of the bilateral group, and 31% of the unilateral group. Comparison of these figures with those at the one-year follow-up period indicates no essential change in the relative degree of effectiveness of each of the three procedures. The relative superiority of bimedial lobotomy is therefore maintained at five years.

Work adjustment. Each patient was rated as to his work adjustment before surgery and at the one and five-year follow-up periods after surgery. "Good" work adjustment ratings were given to those patients who were employed full time and productively, either at home, as in the case of housewives, or in industry in which case they were earning regular salaries. In some instances, a "good" work adjustment rating was assigned to hospitalized patients who were working productively and full time on some industrial project.

Table 2 shows that the bimedial patient group presented more improvement in work activity in the post-operative period when compared with pre-operative work adjustment than either full bilateral or unilateral lobotomy. At five years, 54% of the bimedial cases were rated as showing "good" work adjustment, compared with 33% in the bilateral group and 29% in the unilateral group. Also, note that there was a real increase in number of cases showing "good" work adjustment between one and five years in the bimedial group, as compared to the other two operative groups.

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[2] Data concerning specific symptom changes at one and five-years post-lobotomy in relation to the three types of operation, and details concerning post-operative seizures will be dealt with in another publication by the authors, currently in press. In essence, the incidence of convulsion at five years was not different for the three operative groups, and the symptom changes strongly favor the bimedial operation.

TABLE 1.—FOLLOW-UP OF 116 PATIENTS SUBJECTED TO THREE DIFFERENT LOBOTOMY PROCEDURES

Type of Lobotomy	Significant Improvement		Non-significant Improvement		
	Marked imp.	Mod. imp.	Slight imp.	Unimp.	Morse
Bimedial					
1 year	13 (37%)	8 (23%)	9 (26%)	4 (11%)	1 (3%)
5 years	12 (34%)*(1)	11 (31%)*(1)	4 (12%)	6 (17%)*(1)	2 (6%)
Full bilateral					
1 year	9 (23%)	9 (23%)	12 (31%)	8 (20%)	1 (3%)
5 years	7 (18%)	10 (26%)	12 (30%)*(1)	10 (26%)	0 (0%)
Unilateral					
1 year	9 (21%)	3 (7%)	14 (33%)	12 (29%)	4 (10%
5 years	6 (14%)	7 (17%)*(1)	14 (34%)	14 (33%)*(1)	1 (2%)
Total					
1 year	31 (27%)	20 (17%)	35 (30%)	24 (21%)	6 (5%)
5 years	25 (22%)*(1)	28 (24%)*(2)	30 (26%)*(1)	30 (26%)*(2)	3 (2%)

* Number in parentheses refers to deceased patients showing this rating shortly before death.

TABLE 2.—WORK ADJUSTMENT IN THREE DIFFERENT GROUPS OF LOBOTOMY PATIENTS

Type of Lobotomy	Good	Fair	Poor	Don't Know
Bimedial				
preop.	2 (6%)	8 (23%)	24 (68%)	1 (3%)
1 year	12 (34%)	12 (34%)	11 (32%)	0
5 years	19 (54%)*(2)	4 (12%)	12, (34%)*(1)	0
Bilateral (full)				
preop.	3 (8%)	4 (10%)	31 (80%)	1 (2%)
1 year	10 (26%)	10 (26%)	17 (43%)	2 (5%)
5 years	13 (33%)	5 (13%)*(1)	21 (54%)	0
Unilateral				
preop.	2 (5%)	7 (17%)	33 (78%)	0
1 year	8 (19%)	11 (26%)	23 (55%)	0
5 years	12 (29%)	5 (12%) *(1)	25 (59%)*(1)	0
Totals (116 cases)				
preop.	7 (6%)	19 (16%)	88 (76%)	2 (2%)
1 year	30 (26%)	33 (28%)	51 (44%)	2 (2%)
5 years	44 (38%)*(2)	14 (12%)*(2)	58 (50%)*(2)	0

* Number in parentheses refers to number of patients showing this rating shortly before death.

Changes in clinical rating from one to five years post-lobotomy. "Upgrading" was defined as movement *up* to the "significant" improvement category (moderate or marked improvement) from a lower level of adjustment. "Downgrading" was defined as movement *down* from "significant" improvement to lower levels of adjustment. Altogether, in comparing the one with the five-year follow-up (table 3), upgrading was observed in 13 cases who were "not significantly" improved at one year; and downgrading, in 11 patients who were "significantly" improved. Essentially, only 20% of the patients changed radically, and movement up and down tended to balance.

Table 3 shows no striking difference *in the three operative groups* in movement of cases up or down between one and five years.

Changes in residence between one and five years post-lobotomy. Of interest is the movement of patients from community to hospital and from hospital to community between one and

TABLE 3.—CLINICAL CHANGES BETWEEN ONE AND FIVE YEARS POST-LOBOTOMY

	Number of Cases	Significant (Moderate or Marked Improvement)		Change in Rating Between One and Five Years	
		One year	Five years	Down	Up
Bimedial	35	21	23	2	4
Full bilateral	39	18	17	6	5
Unilateral	42	12	13	3	4
Totals	116	51 (44%)	53 (46%)	11 (9%)	13 (11%)

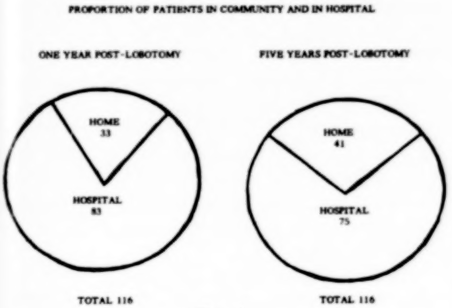

FIG. 1

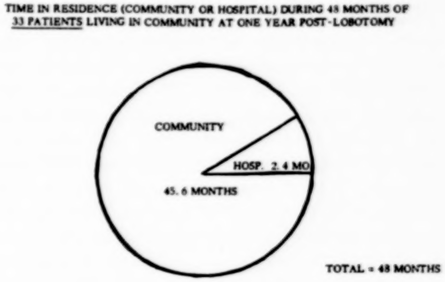

FIG. 2

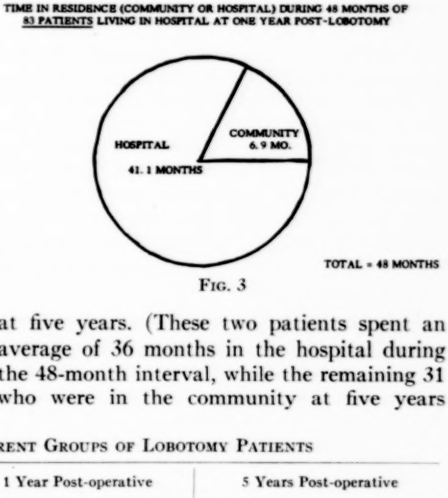

FIG. 3

TABLE 4.—CHANGES IN RESIDENCE FROM ONE TO FIVE YEARS POST-LOBOTOMY

At One Year		At Five Years	
		Community	Hospital
Community	33	31 (94%)	2 (6%)
Hospital	83	10 (12%)	73 (88%)

five years post-lobotomy. Figure 1 shows the total number of patients in the hospital and community at both the one and five-year follow-up period. An actual increase of 8 cases in the community is observed. Table 4 shows that of 33 patients who were in the community at one year, only 2 or 6% were in the hospital at five years. (These two patients spent an average of 36 months in the hospital during the 48-month interval, while the remaining 31 who were in the community at five years

TABLE 5.—RESIDENCE IN THREE DIFFERENT GROUPS OF LOBOTOMY PATIENTS

Type of Lobotomy	Pre-operative		1 Year Post-operative		5 Years Post-operative	
	Community	Hospital	Community	Hospital	Community	Hospital
Bimedial	2 (6%)	33 (94%)	13 (37%)	22 (63%)	17 (49%)*(2)	18 (51%)*(1)
Bilateral (full)	1 (3%)	38 (97%)	11 (28%)	28 (72%)	12 (31%)*(1)	27 (69%)
Unilateral	3 (7%)	39 (93%)	9 (21%)	33 (79%)	12 (29%)*(1)	30 (71%)*(1)
Totals (116 cases)	6 (5%)	110 (95%)	33 (28%)	83 (72%)	41 (35%)*(4)	75 (65%)*(2)

* Number in parentheses indicates number of deceased patients, with their residence at time of death.

altogether spent an average of 0.2 months in the hospital during the 48-month interval.) In the group of 83 patients who were in the hospital at one year, 10 or 12% were in the community at five years. (These 10 patients spent an average of 23.2 months in the hospital between the first and fifth year following surgery, while the other 73 patients who were in the hospital at the end of the fifth year had spent an average of 47.9 months in the hospital.)

Figure 2 shows the average time in residence (either community or hospital) during the ensuing 48 months of 33 patients living in the community at one year post-lobotomy. Altogether, they spent an average of 45.6 out of 48 months in the community and only 2.4 months in the hospital during the four-year interval. Figure 3 shows the average time in residence (community or hospital) during the ensuing 48 months of 83 patients living in the hospital at one year post-lobotomy. Altogether they spent an average of 6.9 months in the community and 41.1 months in the hospital during the 48 months in question. In other words, when a patient is in the community at the end of one year post-lobotomy, he has somewhat better than nine chances out of ten of being in the community at the end of five years; further, the prospect is that he will spend only 72 days in the hospital during the entire 48 months. On the other hand, if a patient is in the hospital at the end of one year, he, too, has about nine chances out of ten of being hospitalized at five years, spending almost seven-eighths of his time during the period in the hospital.

Table 5 compares the residence (community or hospital) of all the patients before operation, and at one and five years after operation. Only 5% of the patients were in the community before operation as compared with 28% at one year post-operative, and 35% at five years post-operative. Comparison of the several operations reveals an increase in the percentage who were in the community at 5 years, as compared to 1 year, for each subgroup, but with no significant difference between them.

SUMMARY AND CONCLUSIONS

This five-year follow-up of 116 lobotomy cases emphasizes the long-term superiority and effectiveness of bimedial lobotomy over full bilateral and unilateral operations in the treatment of chronic intractable psychotic patients. Patients given bimedial lobotomy showed a greater rise in the level of adaptation than was observed with the other two procedures. "Significant" improvement was noted in 65% of this bimedial group at five years contrasted with 44% of the bilateral group and 31% of the unilateral series. In the work area 54% of bimedials showed "good" adjustment (working full time and productively) as compared to 33% of bilateral and 29% of the unilateral cases.

Further inspection of the data reveals that the improvement potential in the bimedial series was not fully realized at the end of one year but continued to emerge during the subsequent four years. This was reflected particularly in the comparative percentage gains between the first and fifth year in work adjustment.

Altogether, improvement after lobotomy tends to be maintained over five years. The over-all improvement figures certainly hold up. Only about 20% of patients change radically in clinical improvement rating, with almost perfect balance between those who move up and down. There are actually more cases in the community at five years than at one year. Any patient in the community at one year has better than nine chances out of ten of being there at five years.

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AN EXAMINATION OF PHENOTHIAZINE DERIVATIVES WITH COMPARISONS OF THEIR EFFECTS ON THE ALERTING REACTION, CHEMICAL STRUCTURE AND THERAPEUTIC EFFICACY

H. E. HIMWICH, F. RINALDI, AND DOROTHY WILLIS[1]

In an attempt to find a method for screening phenothiazine derivatives it seemed appropriate to use the characteristics of chlorpromazine as guideposts. Chlorpromazine is generally accepted as a potent phenothiazine derivative to be used in the treatment of disturbed psychotic patients and patients suffering from anxiety. One of our guideposts was the observation that chlorpromazine alters the reaction to stimuli; the other was based upon the chemical structure of chlorpromazine.

We have previously reported that chlorpromazine in moderate doses prevents the alert electroencephalographic reaction (11). The resting or sleeping pattern induced by chlorpromazine is not altered even by the application of pain. Normally such a nociceptive stimulus changes the resting to an alert pattern (fig. 1). A painful excitation is propagated along nerves from the periphery of the body through the classical pathways and thus is appreciated by the organism. This activity is not inhibited by the drug, but the alerting which is evoked by the pain is prevented. This prevention of the alerting reaction may be the basis for the use of chlorpromazine in the treatment of intractable pain (14, 16). The effect of chlorpromazine may therefore be compared to a functional lobotomy which alters the reaction of the organism to peripheral stimuli. It is not improbable, moreover, that the reaction to painful hallucinations and delusions may be similarly ameliorated (7). In addition the reticular formation sends collaterals to the hypothalamus (6, 15), and a depression of the reticular formation tends to eliminate this source of hypothalamic excitation. This depression will aid in tranquilization in view of the known actions of the hypothalamus in the expression of emotions (1).

The chemical structure of chlorpromazine consists of a phenothiazine nucleus and a side chain, attached to the nitrogen of the nucleus, formed of 3-carbon atoms in a straight chain (table 1). This 3-carbon chain is followed by another nitrogen atom with its other two valences occupied by alkyl groups. An electronegative substitutent, namely chlorine, is found in the 3 position of the nucleus. Taking the chemical structure of chlorpromazine as a basis, Begany, Seifter and their associates (2) tested the hypothesis that active phenothiazine compounds will conform in general with the chemical characteristics of chlorpromazine. Fazekas and his group (3) made clinical evaluations of the same drugs. Using a composite basis, partly chemical and partly electroencephalographic, we assayed a series of phenothiazine compounds. Table 1 presents a model formula of phenothiazine derivatives as well as formulas of the various derivatives studied. Only various structures found in the X, Y and R_1 and R_2 positions are listed.

According to these criteria, derivatives containing either more or less than 3 carbons in a straight chain between the 2 nitrogen atoms should not be effective. Five 2-carbon compounds were studied. The first was promethazine (Phenergan); second, chlorpromethazine (Chlorphenergan); third, diethazine (Diparcol); fourth, Wy 1143, and the fifth, pyrathiazine (Pyrrolazote). The first four of these five blocked the reticular system. Included in this group is promethazine; yet when tested against psychotic patients it failed to exert the prolonged sedative effect of a typical tranquilizing drug and instead had a deep but ephemeral action similar to that of a barbiturate. Chlorpromethazine, diethazine and Wy 1143 have not been evaluated on psychotic patients. In contrast with the above derivatives, pyrathiazine, the fifth substance with a 2-carbon chain, failed to inhibit EEG alerting (7) and was found to be weaker than chlorpromazine in its therapeutic effects on disturbed psychotic patients (5) (fig. 1).

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[1] We are glad to thank Mrs. Helen Owens for technical assistance.

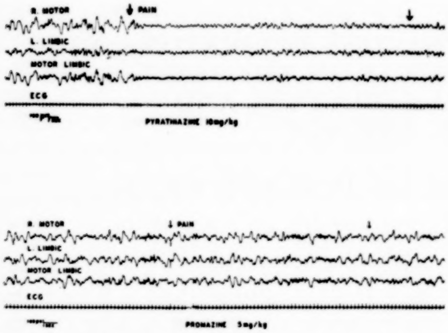


FIG. 1. Effects of pyrathiazine and promazine on the EEG response to pain. The upper group of tracings were obtained with pyrathiazine and the lower ones with promazine. On the left portion of each series of tracings is the pattern characteristic of the resting or sleeping state. Then a painful stimulus is applied to the rabbit's foot. The resting pattern gives way to one of EEG alerting despite the administration of pyrathiazine. The failure of this drug to block the response to pain is presented as an example of the action of those derivatives which do not prevent the pain response. In contrast, with promazine the resting pattern is continued as the characteristic alerting reaction to pain is prevented. This prevention is similar to that observed with other derivatives which block pain. As indicated in the figure, one lead is derived from the right motor cortex, another from the left limbic cortex, and the third is bipolar from both areas.

Wy 1197 and mepazine (Pacatal) contain side chains of more than 3 carbons. Wy 1197, moreover, did not conform to the EEG criteria. In the first place, a 4-carbon straight chain was inserted between the two nitrogen atoms, and in the second, this compound did not block the EEG alerting evoked by pain. Mepazine (7) which interposes four carbons, three being part of a piperidine ring, was not able to block the reticular formation and proved to be less valuable than chlorpromazine in the treatment of disturbed psychotic patients (12) (fig. 1). Thus three derivatives which failed to depress the alerting due to pain were less potent than chlorpromazine in the management of psychiatric patients.

On the other hand, another phenothiazine derivative, Wy 1160, possessing an iso-butyl instead of an n-butyl chain depressed the reticular formation and has been found valuable in preliminary observations in the treatment of disturbed psychotic patients (3). A series of 3-carbon containing compounds which are clinically effective includes promazine (Sparine) (4) (fig. 1), Wy 1107 (3), Wy 1121 (3) and Wy 1137 (3). An interesting case is presented by NP-207 which has a 3-carbon chain, the terminal carbon, however, being part of a piperidine ring. This agent is an excellent tranquilizer (17), blocks the EEG alerting reaction, but may produce temporary untoward effects upon vision. Table 2 presents a list of drugs studied and the dosages required to prevent the alerting response to pain. Incidentally, it may be said that the depression of the response to pain required a larger dose than that to sound. Still larger amounts of these medications were stimulating and facilitated an enduring alert reaction.

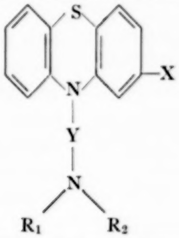
DISCUSSION

We should like to point out in the first place that in presenting our criteria we are not discussing tranquilizing drugs of widely different chemical constitution. Well aware of the pitfalls in the correlation of chemical structure with physiological or pharmacological action, we are limiting ourselves to phenothiazine derivatives.

Despite this limitation even slighter deviations in chemical structure frequently yield different physiologic effects just as they also exhibit varying therapeutic efficacies. For example, we have been making clinical evaluations of three phenothiazine derivatives on the same group of disturbed mental defectives (13). One of these derivatives (promazine) produced convulsions in 7 of 23 individuals who were without a history of previous convulsive seizures. The second derivative (mepazine) evoked convulsions in two patients; only one patient was so affected by the third drug (chlorpromazine). Presumably, many of these mental defectives are brain-injured and that may account for their susceptibility to seizures, a susceptibility which was much less marked in psychotic patients.

Another physiological effect, namely, the bringing on of menstruation, was again a property not shared equally by the same three phenothiazine derivatives (13). Only mepazine brought on the menarche. One woman, 41 years of age, menstruated for the first time in her life, and did so twice during the month of drug administration. Three other patients had menstruated regularly once a month, yet when on the drug two of them menstruated three times

TABLE 1.—MODEL FOR PHENOTHIAZINE DERIVATIVE AND FORMULAS OF VARIOUS DERIVATIVES



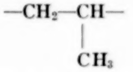
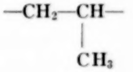
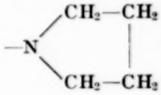
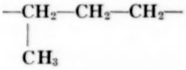
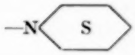
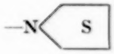
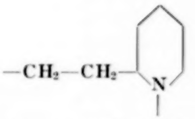
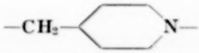
Phenothiazine Designation	X	Y	R₁ R₂
Y = 2 carbons			
1. Promethazine (Phenergan)	H	 $-CH_2-\underset{CH_3}{\underset{\mid}{CH}}-$	$-CH_3-CH_3$
2. Chlorpromethazine (Chlorphenergan)	Cl	 $-CH_2-\underset{CH_3}{\underset{\mid}{CH}}-$	$-CH_3-CH_3$
3. Diethazine (Diparcol)	H	$-CH_2-CH_2-$	$-C_2H_5-C_2H_5$
4. Pyrathiazine (Pyrrolazote)	H	$-CH_2-CH_2-$	
5. Wy 1143	H	$-CH_2-CH_2-$	$-CH_3-CH_3$
Y = 3 carbons			
1. Chlorpromazine (Thorazine)	Cl	$-CH_2-CH_2-CH_2-$	$-CH_3-CH_3$
2. Promazine (Sparine)	H	$-CH_2-CH_2-CH_2-$	$-CH_3-CH_3$
3. Wy 1160	H	 $-\underset{CH_3}{\underset{\mid}{CH_2}}-CH_2-CH_2-$	$-CH_3-CH_3$
4. Wy 1107	H	$-CH_2-CH_2-CH_2-$	$-C_2H_5-C_2H_5$
5. Wy 1121	H	$-CH_2-CH_2-CH_2-$	
6. Wy 1137	H	$-CH_2-CH_2-CH_2-$	
7. NP-207	Cl		$-CH_3$
Y = more than 3 carbons			
1. Wy 1197	H	$-CH_2-CH_2-CH_2-CH_2$	$-CH_3-CH_3$
2. Mepazine (Pacatal)	H		$-CH_3$

TABLE 2.—DOSAGE OF PHENOTHIAZINE DERIVATIVES REQUIRED TO DEPRESS AND TO STIMULATE THE RETICULAR SYSTEM

Phenothiazine Derivatives Tested	Depression of the Reticular System	Stimulation of the Reticular System
	mg./kg.	*mg./kg.*
2-carbon chains:		
1. Promethazine	5–10	12–20
2. Chlorpromethazine	10–12	15–20
3. Diethazine	4–8	12–20
4. Pyrathiazine	no block of pain	20–30
5. Wy 1143	7–10	large amounts
3-carbon chains:		
1. Chlorpromazine	3–6	12–18
2. Promazine	3–7	15–20
3. Wy 1160	5–9	19–24
4. Wy 1107	7.5–10	12–20
5. Wy 1121	5–10	12–20
6. Wy 1137	5–10	12–20
7. NP-207	7.5–12	no stimulation up to 35
more than 3 carbons:		
1. Wy 1197	no block of pain	13–20
2. Mepazine	no block of pain	15–20

during the month, and the third patient menstruated twice. It is therefore not surprising to find that some of these derivatives failed to inhibit the reticular formation and to alter favorably the reaction of the patient to painful stimuli.

Thus far every phenothiazine derivative which is highly active in the amelioration of disturbed patients has also blocked the alerting EEG reaction. The converse, however, does not hold; for example, some of the 2-carbon chain derivatives inhibit the reticular system yet are not effective clinically. This suggests that the depression of the reticular formation has a beneficial effect on disturbed patients, but that additional actions are necessary to produce tranquilization. Reticular inhibition is only part of the therapeutic mechanism of tranquilization. On the other hand, all the 3-carbon chains examined have blocked the reticular formation and in addition produced favorable clinical results. These facts lead to the suggestion that 3-carbon phenothiazine derivatives which check reticular activation should be used in clinical trials for new drugs.

If we might venture a temporary hypothesis, perhaps a 3-carbon-nitrogen chain may be necessary to fit a receptor. It is interesting to point out that serotonin has a side chain containing a terminal nitrogen atom and a 2-carbon chain which in turn is attached to a carbon of the indole nucleus.

In this investigation we used rabbits to determine the effects of various phenothiazine derivatives on the alerting response to pain and observed that the prevention of this response was a characteristic shared by many but not all of the phenothiazine derivatives studied. Whether or not such a prevention applies to man is of importance in the interpretation of our results. A suggestion that blocking of the reticular formation may also occur in man comes from the use of chlorpromazine in the treatment of intractable pain (14, 16), despite the relatively smaller dose used in patients. Another suggestion comes from the work of Liberson who noted that in patients with an initially low alpha continuity the administration of chlorpromazine increased the continuity from 40 to 70 per cent. This, too, may be taken as indicating depression of the reticular formation (9).

When the dosages of these phenothiazine compounds are gradually raised above the values producing depression and presented in table 2, a reversal is revealed. The reticular system is stimulated, and the alerting reaction is facilitated (11). With still larger amounts of these agents convulsions ensue (8). Preston (10) also observed the facilitation of the arousal pattern following stimulation of the medial reticular formation and with adequate dosage grand mal type of seizure discharges in cats. He reports that the amygdaloid nucleus is especially sensitive to the effects of that drug and may therefore be an initial site of the convulsions.

SUMMARY AND CONCLUSIONS

A series of phenothiazine derivatives was examined to determine the effect on the reticular formation. Three derivatives which failed to block the alerting reaction to pain were inferior to chlorpromazine in the management of disturbed psychotic patients. It is therefore suggested that failure to depress the alerting reaction may be used as a screening procedure

of new phenothiazine derivatives. But the converse does not hold, and their ability to inhibit alerting is not an adequate sign of therapeutic efficacy. In general, phenothiazine derivatives with 3 carbons in a straight chain are more effective tranquilizers than others with a greater or lesser number of carbons.

We wish to thank the following organizations for their generous supplies of phenothiazine derivatives: Smith, Kline and French Laboratories (Thorazine); Warner-Chilcott Laboratories (Pacatal); Wyeth Laboratories (Sparine, Chlorphenergan and all Wy drugs); Sandoz Pharmaceuticals (NP-207); Upjohn Company (Pyrrolazote); Merck and Company (Diparcol); Recip, Stockholm (Phenergan).

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NOR-EPINEPHRINE-LIKE AND EPINEPHRINE-LIKE SUBSTANCES IN RELATION TO HUMAN BEHAVIOR[1]

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The adrenal medulla secretes at least two hormones, nor-epinephrine and epinephrine. Some investigators think that nor-epinephrine is principally secreted by the post-ganglionic cells. For many years, psychophysiological studies relative to this gland were largely confined to experiments elucidating the role of epinephrine in bodily physiology, especially in relation to emotional changes. In 1947, Tainter, Tuller and Laduena (51) successfully made in the laboratory an optically active form of nor-epinephrine. This substance had long been suspected of being a sympathomimetic substance, but since only a racemic mixture of the substance which was physiologically inert was available, this hypothesis could not be tested. Once, however, the optically active forms of the substance were available, confirmation of its secretion by the adrenal medulla and elucidation of many of its physiological properties were rapidly accomplished.

Epinephrine and nor-epinephrine elicit markedly different physiological reactions in the body. Epinephrine may be characterized as a "metabolite" because of the widespread physiological reactions it evokes, in many different systems, such as increased oxygen consumption of the brain, increase in pulse rate and cardiac output, decreased peripheral resistance, relaxation of the bronchioles, decrease in the clotting time of the blood, changes in glucose metabolism, etc. On the other hand, nor-epinephrine has no such widespread system effects; its principal effect being to increase peripheral resistance throughout the body.

This paper is a summary and a review of our own work related to nor-epinephrine and epinephrine. Reference will be made to pertinent work of other investigators. The work will also be discussed in a theoretical framework. Our investigations were accomplished over a period of ten years, in association with many colleagues in many disciplines among which were the social sciences, physiology, medicine, psychiatry and biostatistics. Major contributions to the work were made by members of the Department of Social Relations, Harvard University, and of the Department of Biostatistics, Harvard School of Public Health. References to the individual's work will be referred to and listed in the bibliography.

Techniques used in these studies. It is only within the past year, by the culmination of the work of Weil-Malherbe (52), Aronow and Howard (3) and Elmadjian, Hope and Freeman (14), that reliable methods of the assessment of the nor-epinephrine/epinephrine ratio in blood and/or urine were possible. Due to the technical difficulties and the recentness of the development of the method, few reports have as yet appeared in the literature using these techniques of direct measurement. This necessitated the use in our work of a physiological method of assessing, on a qualitative basis, whether or not a given physiological reaction represented predominantly a nor-epinephrine-*like* or predominantly an epinephrine-*like* reaction. When the reaction of a subject was similar to that which can be obtained by the intravenous injection of epinephrine in healthy subjects during non-stressful situations, it was labeled an epinephrine-*like* reaction; when the reaction was similar to that which can be obtained by the intravenous injection of nor-epinephrine, it was classified as a nor-epinephrine-*like* reaction. The two physiological methods used by us were the systolic blood pressure reaction following the drug mecholyl and the cardiovascular reaction as measured by the systolic and diastolic blood pressure, the pulse, and the ballistocardiographic measures of IJ, IJ x p,

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[1] The work reported here was supported in part under a grant from the Supreme Council, 33rd Degree, Scottish Rite, Northern Masonic Jurisdiction, U. S. A., through the National Association for Mental Health; in part under Contract AF 33(038)20142 from the School of Aviation Medicine, Randolph Field, Texas.

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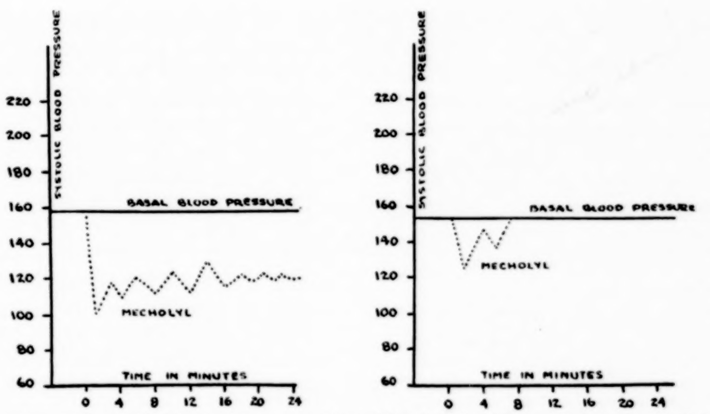

FIG. 1. Two types of systolic blood pressure reactions following the drug mecholyl. On the left is a typical Group VI reaction interpreted on the basis of previous research as indicating excessive secretion of an epinephrine-*like* substance. On the right is a typical Group II-III reaction interpreted on the basis of previous research as indicating excessive secretion of a nor-epinephrine-*like* substance.

and P/IJ x p. The importance of the mecholyl response as a measure of autonomic reactivity was described by Deutsch and Nadell (12). Reference to the technical methods used by us in relating the mecholyl reaction and the cardiovascular pattern to the reactions obtained by the injection of nor-epinephrine and epinephrine will not be elaborated here. Reference is made to the following papers which describe the methods in detail (27, 30).

The adrenalin-mecholyl test, reported by us in 1948 (24) as a prognostic test for mentally ill patients, provided for the classification of the blood pressure reactions of subjects into seven different groups. Considering the mecholyl blood pressure reaction alone, two of the groups occur frequently, Groups II-III and VI. The Group II-III mecholyl response was characterized by the following blood pressure reaction: Minimal fall, small area under the curve, and the return of the blood pressure to the pre-injection level within a few minutes. The Group VI blood pressure response was characterized by a marked fall, large area under the curve and a failure to return to the pre-injection level during the 25-minute observation period (fig. 1).

On the basis of the extensive physiological experiments referred to previously (27, 30), we reached the following conclusion: When the blood pressure was elevated, as a result of emotion, a Group II-III reaction indicated evidence of excessive secretion of a nor-epinephrine-*like* substance; a Group VI response, an excessive secretion of an epinephrine-*like* substance.

Elmadjian, Hope and Freeman (14), using a bio-assay method of determining the amounts of nor-epinephrine and epinephrine in the urine confirmed the relationship of the type of mecholyl reaction to the nor-epinephrine/epinephrine secretion. They found that the "area" under the mecholyl curve correlated highly with the nor-epinephrine/epinephrine ratio. When the area was small, the nor-epinephrine/epinephrine ratio was high; when the area was large, the nor-epinephrine/epinephrine ratio was low.

This work of Elmadjian, Hope and Freeman gave confirmatory evidence that the mecholyl reaction was an indicator of the type of preponderant adrenal medullary secretion. Using the other method involving certain cardioballistographic variables, both Hickam, Cargill and Golden (38) and Goldenberg *et al.* (33) reported similar findings.

Despite the evidence in the literature that these methods were indicators of the relative dominance of one secretion over the other, in all of our references to our work we will use the suffix *like* after epinephrine and nor-epinephrine and shall continue to do so until almost all of our experiments are repeated using direct measurements of these substances in the blood.

Nor-epinephrine-like and epinephrine-like substances and emotions. In three different reported investigations, we accumulated evidence that different emotions were accompanied by different physiological reactions. *Anger Directed Outward* was accompanied by physiological evidence of excessive secretion of a nor-epinephrine-*like* substance, whereas *Anger Directed Inward* and *Anxiety* were accompanied by physiological evidence of excessive secretion of epinephrine-*like* substances. The three reported investigations were the following:

Funkenstein (21, 22) found that angry paranoid patients had physiological evidence on the basis of their mecholyl reactions of excessive secretion of nor-epinephrine-*like* substances, whereas depressed patients (*Anger Directed Inward*) had physiological evidence of excessive secretion of nor-epinephrine-*like* substances.

Our second studies were carried out on medical students during acute real life stressful situations (22). Students who reacted with *Anger Directed Outward* showed physiological evidence as determined by both mecholyl and cardiovascular reactions of excessive secretion of nor-epinephrine-*like* substances; those who reacted with either *Anger Directed Inward* or *Anxiety*, evidence of excessive secretion of epinephrine-*like* substances.

Still further experiments dealt with the reactions of healthy subjects during contrived laboratory stress-inducing situations (27). Again, those reacting to the situation with *Anger Directed Outward* showed excessive secretion of nor-epinephrine-*like* substances; those reacting with *Anger Directed Inward* or *Anxiety*, physiological evidence of excessive secretion of epinephrine-*like* substances. Using a bio-assay method for determining the hormones, Elmadjian (13) confirmed the relationship of aggressive behavior and anxiety to different adrenal secretions.

All of this evidence strongly suggested that that the emotions manifest during acute emergency reactions were separable into component parts with different physiological reactions.

Neurophysiological mechanisms. The mechanisms by which different emotions activate different physiological reactions need elucidation. If we assume that the chemical substance which activates the physiological pattern seen during *Anger-Out* is in fact nor-epinephrine and that the chemical substance which activates the physiological pattern seen during *Anger-In* or *Severe Anxiety* is in fact epinephrine, the question immediately arises as to the method by which different emotions evoke different secretions from the adrenal medulla. Recent work in neurophysiology throws some light on a possible mechanism. A fine review of this entire problem is that of Cleghorn (10). Gellhorn (31, 32, 47) has made extensive studies of the relationship of the mecholyl reaction to hypothalamic function.

Folkow and von Euler (18) and Redgate and Gellhorn (48) reported that in the anesthetized animal stimulation of certain hypothalamic areas produced an almost pure secretion of nor-adrenalin, whereas stimulation of other areas in the hypothalamus produced an almost pure secretion of adrenalin. This work, coupled with other physiological evidence, led to von Euler's theory that there are two types of cells in the adrenal medulla, one secreting nor-adrenalin and one secreting adrenalin, and that they are separately enervated and separately represented in the hypothalamus. Although most neurophysiologists do not believe that the adrenal medulla contains two types of cells, experimental evidence is accumulating that the secretion of nor-epinephrine and epinephrine is separately represented in the hypothalamus. Whether stimulation of these different areas leads to different secretion by the intensity of the stimulus or some mechanism from the hypothalamus to the adrenal is unknown. Hess and Abert (37) reported that stimulation of certain areas in the anterior hypothalamus in animals produced behavior interpreted as fear, whereas stimulus in certain areas in the posterior hypothalamus resulted in behavior interpreted as aggression. The areas, whose stimulation by von Euler produced nor-epinephrine, were similar to those which Hess stimulated to produce aggressive behavior; the areas, whose stimulation by von Euler produced epinephrine, were similar to those which Hess stimulated to produce flight in animals.

This work suggests that different emotions activate different areas in the hypothalamus which in turn evoke different secretions from the adrenal medulla. Still open is the mechanism by which different emotions activate different hypothalamic areas and how these areas activate different secretions from the adrenals.

Much more experimental work is needed in this area.

There is other recent neurophysiological work in animals which bears directly on the experiments reported in this project. As the result of extensive investigations, Holtz and Schumann (40) stated the theory that nor-epinephrine represents the resting secretion of the adrenal medulla, whereas epinephrine is secreted only in response to an emergency reaction. Confirmatory evidence of this was the finding in one of our experiments (28) that when the students were not upset by a stress experiment and reported that they had experienced no emotion, a nor-epinephrine-*like* pattern and a physiological reaction of minimal intensity occurred. Under such circumstances an emergency reaction was not necessary; only the resting secretion was used. In contrast to this, when the men reported either *Anger Directed Inward* or *Severe-Anxiety,* an emergency reaction occurred, epinephrine was secreted, and a very intense physiological reaction took place. Epinephrine also evoked many widespread physiological reactions throughout the many systems of the body.

The physiological accompaniments of *Anger Directed Outward* were similar to those of *No Emotion*, i.e., a nor-epinephrine-*like* pattern and a minimal intensity of physiological reaction. In the frame of reference that nor-epinephrine represents the resting secretion of the adrenal medulla and that epinephrine, the emergency secretion, an explanation is needed as to why *Anger Directed Outward* does not evoke an emergency secretion but *Anger Directed Inward* and *Severe-Anxiety* do. The most probable explanation is the difference in the *objects* of the emotions. In the case of *Anger Directed Outward,* the objects were others so that the self was not threatened. Both in the *Anger Directed Inward* and *Severe-Anxiety* Groups, impulses presented a threat to the self so that an emergency reaction was necessary. The threat to the self in the former group was the retroflexed anger; in the second group, conflicts about hostile impulses with resulting fear of one's own hostile impulses or the assignment of such impulses to the experimenter with resulting retaliatory anxiety. *Anger Directed Outward*, as it does not threaten the self, does not need an emergency reaction, so a minimal reaction with a nor-epinephrine-*like* pattern occurs (the resting secretion of the adrenal medulla); the self-related emotions of *Anger Directed Inward* and *Severe-Anxiety* do pose a threat to the self and necessitate emergency reactions and the secretion of epinephrine from the adrenal which represents the emergency reaction.

Cannon's fight-flight reaction. The finding of specific physiological patterns for specific emotions differed from Cannon's work (9). He taught that the anger and fear of the Fight-Flight reaction were admixed, inseparable, and always associated with secretion of adrenalin. However, he could not explain all of his findings on the basis of adrenalin alone and postulated two other sympathomimetic substances, sympathin E and sympathin I. As a result of recent experimentation, there is good agreement among physiologists that sympathin E and nor-epinephrine are identical. Wolff and his coworkers (53) at the New York Hospital accumulated much confirmatory evidence that the Fight-Flight emotions were separable. They showed that in various organs, such as the stomach, colon and the nose, different emotions evoked different physiological reactions. Ax (4) found different physiological reactions as determined by the polygraph during anger and fear. These experiments suggest that the Fight-Flight reactions may well be separated into component emotions with different physiological accompaniments.

Parallel data in animals. Related studies of the adrenal medullae of animals were made by Goodall (34). Most of his work was carried out in Africa where the animals were shot and their adrenal medullae analyzed chemically for the relative proportions of epinephrine and nor-epinephrine. His findings may be seen in table 1.

Several observations are of interest: Domestic animals have proportions of adrenal substances comparable to those of man. In general, herbiverous animals, such as the rabbit and the antelope, which depend principally on flight for survival, have a higher adrenalin/nor-adrenalin ratio than do carniverous animals, such as the lion, which depend for survival primarily on aggressive behavior. This suggests that aggressive and flight behavior in both animals and in man were associated with the same types of adrenal medullary secretion. Although a given species

TABLE 1.—EPINEPHRINE AND NOR-EPINEPHRINE CONTENT IN SUPRARENAL GLANDS FROM VARIOUS ANIMALS

Animal	Nor-epinephrine	Epinephrine	Per Cent Epinephrine
	mg./gm.	*mg./gm.*	
Baboon	0	0.83	100
Rabbit	0–0.2	0.4	94–100
Guinea pig	0.01–0.07	0.5	88–98
Rat	0.16	0.9	84
Man	0.05–0.1	0.3–0.8	80–90
Cow	0.5–1.3	1.8–3.3	75–85
Zebra	0.1–0.3	1.4–1.9	70–85
Sheep	0.4–0.9	0.8–1.5	55–80
Dog	0.5	1.6	76
Impala	0.2	0.6	75
Grant gazelle	0.3–0.4	0.6–0.7	65
Thompson gazelle	0.36	0.56	61
Wildebeest	0.6	0.83	57
Squirrel	0.1	0.1	50
Cat	0.4–0.8	0.4–0.8	40–60
Toad	1.2–2.4	1.2–2.7	40–60
Lion	0.3	0.2	40
Dogfish	6.0	3.0	30
Whale	0.5–2.5	0–1	0–50

The nor-epinephrine and epinephrine content of the adrenal medullae of various animals (von Euler, U. S.: Distribution and possible physiologic functions of epinephrine and nor-epinephrine. In *Shock and Circulatory Homeostasis.* Editor: H. D. Green, New York: The Josiah Macy Jr. Foundation, 1953).

of animal can show more than one type of behavior, their one principal behavior is largely species determined and closely related to structure. Man, being higher up the evolutionary scale, has the *capacity* to react in a variety of ways. We would state the theory that man, being higher up the evolutionary scale, contains within himself both the "lion" and the "rabbit", and his *habitual* or most frequent method of reacting is determined by his early childhood experiences. Confirmatory of the importance of the family in determining the habitual acute emotional reactions of the subjects were the high correlations we obtained between the perceptions of their families by subjects and their reactions during stress. These will be referred to in more detail later (28, 43).

Psychological and physiological development. There is considerable psychological evidence that *Anger Directed Outward* in healthy individuals is characteristic of an earlier period of development than *Anger Directed Inward* and *Severe-Anxiety* (conflicts over hostile impulses). The *Anger Directed Outward* reaction occurs early in life, and it is only as the child grows older and the acculturation process takes place that the necessity for retroflexing anger on the self or conflicts between hostile impulses and culturally acceptable behavior leading to anxiety occur. Since *Anger Directed Outward* was found to be associated with nor-epinephrine and *Anger Directed Inward* and *Severe-Anxiety* with epinephrine in adults, it would be expected that since *Anger Directed Outward* represented a reaction characteristic of an earlier stage of development, the adrenal medulla at birth and in early infancy would contain predominantly nor-epinephrine and that, as the child developed, epinephrine would then be secreted. This was exactly the findings of Hokfelt (39) and Shepherd and West (50). Both the adrenal of the fetus and the adrenal of animals at birth contained predominantly nor-epinephrine with epinephrine being gradually added as the child develops, eventually becoming the dominant secretion. Thus, psychological and physiological development parallel each other.

Psychological and physiological regression. It is generally accepted from a psychological standpoint that the paranoid patient represents a deeper level of regression than does the depressed patient. The physiological findings reported here parallel these psychological observations. The adrenal medulla at birth contains predominantly nor-epinephrine with epinephrine becoming the predominant secretion as a later stage of development is reached (39). Previously we reported that most paranoid patients had evidence of excessive secretion of nor-epinephrine-*like* substances, whereas most depressed patients had evidence of excessive secretion of epinephrine-*like* substances. Thus, the paranoid patients whose illness is characteristic of an earlier stage of development than that of depressed patients show a physiology characteristic of an earlier phase of development than shown by depressed patients. Huntington (41) found that patients showing excessive secretion of nor-epinephrine-*like* substances showed on psychological testing evidence of deeper regression than patients showing excessive secretion of an epinephrine-*like* substance. These findings, coupled with the previous findings relating to parallels in psychological and physiological development, lead to this hypothesis: As the psychotic patient's regression reverses the psychological stages of early development, a parallel reversal of the physiological stages of early development also takes place.

Development, regression and evolution. Another glance at the table on the nor-epinephrine/epinephrine ratio of the adrenal medullae of various species of animals suggests that the sea animals have a much higher ratio of nor-epinephrine in relation to epinephrine than do land animals. These animals are lower on the evolutionary scale than the others. This again suggests the hypothesis, which is in this case founded on very little evidence, that the psychological and physiological development of the child recapitulates the evolutionary development, and that regression not only reverses the stages of early development of the child but also reverses the stages of evolutionary development. It is possible, in this frame of reference, to also state the hypothesis that the psychological evolutionary process of the child is completed during early childhood in the family. Ferenczi (17) stated this same idea in slightly different terms. While just a hypothesis, it is intriguing and should be considered in the light of both Cannon's and Rado's (46) thoughts about acute emergency behavior in the light of evolutionary development.

Relationship to prognosis in mental illness. The adrenalin-mecholyl test, first described by us in connection with prognosis in psychiatric patients (24), had been the subject of extensive studies by others in connection with a variety of different forms of treatment (1, 2, 8, 11, 32a, 42, 45, 49, 51a). Originally seven different groups representing different blood pressure reactions were described. In this report we will confine our discussion to Groups II-III representing excessive secretion of a nor-epinephrine-*like* substance and Group VI representing excessive secretion of an epinephrine-*like* substance.

In terms of electric shock treatment, in both our studies and those referred to above, approximately 90 per cent of patients showing excessive secretion of an epinephrine-*like* substance responded to such a treatment, whereas only *14* per cent of those showing excessive secretion of a nor-epinephrine-*like* substance responded.

In the case of insulin, patients whose autonomic findings were interpreted as indicating an excessive secretion of an epinephrine-*like* substance showed a higher improvement rate than those whose autonomic findings were interpreted as indicating an excessive secretion of nor-epinephrine-*like* substances.

In the case of lobotomy, Greenblatt and Solomon (35) found that patients in Group VI (epinephrine-*like*) showed a higher percentage of improvement than patients with a Group II-III (nor-epinephrine-*like*) reaction.

In studies of the effect of intravenous ether which was controlled by intravenous saline, over 50 per cent of the cases showing excessive secretion of an epinephrine-*like* substance recovered from their psychoses, whereas only *12* per cent of those showing excessive secretion of a nor-epinephrine-*like* substance recovered (29).

Spontaneous remission and recoveries with psychotherapy were much higher in those showing physiological evidence of excessive secretion of epinephrine than those showing excessive secretion of nor-epinephrine (23, 45a).

These studies all show that patients with evidence of excessive secretion of an epinephrine-*like* substance show a much higher rate of recovery regardless of the method of treatment than patients with excessive secretion of a nor-epinephrine-*like* substance.

Relationship to tranquilizing drugs. Ayd (6), Bray and Funkenstein (7), Schneider (49), and others have shown that the effect of either chlorpromazine and Serpasil on the autonomic reaction to mecholyl is to increase the reaction to the drug in terms of blood pressure. In terms of the underlying physiology, this suggests that the effect is to change the medullary secretion toward a higher epinephrine/nor-epinephrine ratio. Since changes in this ratio in the same direction are associated with depressions, these physiological changes suggest that these are parallel changes to those reported in the literature of patients developing depression when treated with these drugs (16). Ayd (5) reported the admission to hospitals of large numbers of patients with psychotic depressions produced by the drug reserpine.

Relationship to psychological studies. Extensive studies of the results of psychological tests to the results of these autonomic tests were carried out in our laboratories and elsewhere. These are reported only briefly.

Huntington (41) studied two groups of psychiatric patients chosen on the basis of their autonomic physiology for psychological testing. One group previously designated as autonomic Group II-III (interpreted on the basis of previous experimentation as indicating excessive secretion of a nor-epinephrine-*like* substance), and another group previously designated as autonomic Group VI (interpreted on the basis of previous experimentation as indicating excessive secretion of an epinephrine-*like* substance) were given The Thematic Apperception Test, the Rorschach Test, and a Sentence Completion Test. The psychologist was unaware of the physiological grouping of the subjects. The psychological results were then compared with the physiological grouping of the subjects, and the following differences in the dynamic constellations were found. (Hypotheses in which the differences between the groups were not statistically significant are omitted here.)

1. Group VI exceeded Group II-III in manifestations of overt anxiety, while Group II-III exceeded in anxiety in fantasy ($P < .001$).
2. Group II-III exceeded Group VI in the use of adjustive mechanisms of regression ($P < .01$), denial in fantasy and act ($P < .001$), and projection ($P = .05$). Group VI exceeded Group II-III in the use of compulsive mechanisms ($P = .01$), introjection ($P < .01$) and dehumanization ($P = .02$).
3. Group II-III exceeded Group VI in the direct expression of aggression toward the world ($P < .001$) Group VI exceeded Group II-III in turning the aggression inward, on the self ($P < .001$).
4. Group II-III exceeded Group VI in the manifestations of oral agression ($P = .01$).
5. Group II-III exceeded in the expression of strong love-hate ambivalence involved in relationships with significant figures ($P < .001$). Group VI exceeded in the introjection of these conflicts and thus also in the manifestations of guilt ($P < .01$).
6. Group II-III exceeded Group VI in experiencing feelings of threat from mother figures and in directing aggression toward women ($P = .03$).
7. Group II-III exceeded Group VI in frequency of fantasied relationships which are aggressive, regressive and dependent ($P = .01$). Group VI exceeded Group II-III in fantasied relationships showing a desire for warmth and close contacts ($P = .01$).
8. Group VI exceeded Group II-III in fantasies of being deserted and having lost a love object ($P < .001$).
9. On a more conscious level, Group II-III exceeded in the expression of desire for passive, dependent relationships ($P < .001$). Group VI exceeded in wishes to be mature and independent, and expressions of anger when this is not allowed ($P < .001$).
10. Group VI exceeded Group II-III in expression of inadequacy feelings and an unflattering self-picture ($P < .001$).
11. For Group II-III there was less differentiation of sex roles ($P = .01$). Group VI exceeded Group II-III in expression of guilt feelings in relation to sexuality ($P < .01$).
12. Group II-III exceeded Group VI in the expression of primitive annihilation fears and sensations of bodily distortion ($P < .001$).
13. Group VI exceeded Group II-III in the presence of depressive affect ($P < .001$).

Miller (44), using a battery of psychological tests, found that marked changes occurred in these measures when there was a change in the blood pressure reaction following mecholyl. Such parallel psychological changes did not occur when the physiological changes remained static.

Funkenstein, King and Drolette (28) found many differences, using psychological and sociological techniques, between healthy subjects who showed during acute stress evidence of excessive secretion of nor-epinephrine-*like* substances as compared with those showing evidence of excessive secretion of epinephrine-*like* substances. These psychological and sociological differences were more closely related to the type of emotion reported by the subjects than to type of adrenal substance. These investigations are summarized in table 2.

DISCUSSION

The mecholyl test, on the basis of several physiological experiments, was interpreted by us as an indicator of the nor-epinephrine/epinephrine ratio. This was confirmed by Elmadjian, Hope and Freeman (14) using bioassays of the adrenal hormones.

This test has had its principal clinical usefulness in selecting methods of treatment for psychiatric patients. A number of investigators reported its usefulness in deciding on the feasibility of various somatic treatments. We would like to call attention and to emphasize here that, in a broad general sense, these tests are related to prognosis regardless of the type of treatment. Even when patients showing excessive secretion of an epinephrine-*like* substance were "treated" with normal

TABLE 2

	Nor-epinephrine-like		Epinephrine-like	
1. Emotion	No emotion	Anger directed outward	Anger directed inward	Anxiety
2. Object	No object	Object—others	Object—self	Object—self and others (conflicts over hostile impulses—retaliatory anxiety)
3. Perception of parents	Father—authority, role model, affection Mother———— Father fulfills three roles (ambivalent relationship with father)	Father—authority, role model Mother—affection Marked difference in roles of parents (boy's relationship with father poor)	Father—authority, role model Mother—affection Little difference in roles of parents (boy's relationship with father good)	Father———— Mother—authority, role model, affection Mother fulfills three roles (ambivalent relationship with mother)
4. Internal concept of self	Small difference between Best Self and Worst Self	Large difference between Best Self and Worst Self	Moderate difference between Best Self and Worst Self	Small difference between Best Self and Worst Self
5. Thematic apperception test	A. Large quantity of aggression B. Consequences of aggression—guilt C. Aggression toward men D. Punishment by men using physical or verbal means	A. Little aggression B. Consequences of aggression—not calamitous C. Aggression toward men D. Punishment by men using physical or verbal means	A. Large quantity of aggression B. Consequences of aggression—punishment and guilt C. Aggression toward men and *women* D. Punishment by men and *women* using fear of loss of love	A. Mixed amounts of aggression B. Consequences of aggression—physical injury to self C. Aggression toward women D. Punishment by women using *physical* means and loss of love
6. Social class	Mixed	Mixed	Upper upper (Old New England family)	Mixed

The psychological and sociological correlates of excessive secretion of epinephrine-like and nor-epinephrine-like substances during acute stress in healthy subjects (Funkenstein, D. H., King, S. H., and Drolette, M. E.: *Mastery of Stress*. Harvard University Press (In press).

saline, they, too, showed a much higher incidence of recovery than patients with excessive secretion of nor-epinephrine-*like* substances. Recovery without planned treatment occurred most frequently in this same particular group. The poor recovery rate in the psychoses is not only a function of the type of treatment but also of the type of patient. These tests also suggest that it is possible to harm patients if certain somatic treatments are used indiscriminately. Of some interest was the report by Clemens (11), who found that patients with mecholyl reactions which indicated a good prognosis in mental illness also indicated a good prognosis in carcinoma; mecholyl reactions which indicated a poor prognosis in mental illness also indicated a poor prognosis in carcinoma. This is intriguing and merits further investigations.

Paralleling the physiological changes incident to recovery from a psychosis, there is a parallel psychological change. When there are psychological changes in the patient and the accompanying physiological changes fail to occur, or when there are physiological changes without the accompanying psychological changes, the patient almost always relapses. This holds true regardless of treatment, whether by psychotherapy or somatic treatment or changes not induced by planned treatment (25).

The many correlations obtained between the psychological and physiological studies serve to emphasize that, in speaking of prognosis of psychotic patients, findings by investigators in different disciplines merely refer to different methods of observing the same phenomenon. For example, it is well known by psychoanalytical studies that the deeper the stage of regression in psychotic patients, the poorer the prognosis. Thus, the paranoid patients have a poorer prognosis than depressed patients. On a physiological level, patients with excessive secretion of nor-epinephrine, which represents a secretion characteristic of an earlier stage of development, have a poorer prognosis than patients showing evidence of excessive secretion of epinephrine, which is characteristic of a later period of development. Here is a parallel between psychological and physiological regression, both representing in actuality one process. The correlation here is between the observers and their methods of observation rather than "parts" of patients. When it is stated that prognosis is poor when patients show deep psychological regression or that prognosis is poor when there is excessive secretion of nor-epinephrine, different disciplines refer to the same process.

Again, in seeking the *determinants* of the type of reaction encountered, several viewpoints are possible. In seeking the antecedents of the type of excessive secretion encountered in a given subject, it is possible to look for an explanation in either psychological, physiological or sociological terms. If a *physiological* explanation is sought, one may refer to studies by Folkow and von Euler (18) or Gellhorn (32) or Cleghorn's review (10) concerning the hypothalamic explanation for this difference. If we seek a *psychological* explanation for this, we may relate it to the type of emotion expressed, as different emotions are related to different types of secretions. Beyond the emotional response as the determinant of the secretion, we can look a step further, where we may see the effect of the fantasies of which the subjects are unaware, concerning the expression of aggression and its consequences which explain the difference in the type of emotion expressed. Still further, a close relationship can be found between Concept of Self, body image and the perception of parents (28). Seeking a *sociological* explanation, high correlations were obtained between the type of secretion and social class (28). The higher the social class, the more apt the secretion to be adrenalin. This is further related to the high incidence of intropunitive reactions in the upper class as shown by Henry (36) and others (20).

These findings, physiological, psychological and sociological, all represent different aspects of the personality from different frames of reference.

Evidence of excessive secretion of nor-epinephrine and epinephrine can be found in both psychotic patients and in healthy subjects, but there is a difference. The evidence of excessive secretion of these hormones can be found in the patients on the wards without external stressful situations, whereas, in the healthy subjects, excessive secretion is found only when the subject is under stress. For example, depressed patients on a ward will show evidence of excessive secretion of epinephrine, whereas students whose habitual style of reacting during acute stress is depression will show excessive secretion of epinephrine only during such acute stressful times.

This brings up the crucial question of the difference between the "sick" and the "well". We would suggest the hypothesis that the difference lies largely in the handling of the situation on a time continuum. For example, healthy subjects whose habitual reaction to acute stress is depression are able as time passes to master the situation; the emotion abates, and the physiology returns to its pre-stress level. On the other hand, depressed patients show a failure in mastery so that the reaction becomes sustained, the physiology increases in intensity and the clinical reaction type becomes recognizable. The crucial factor is the ability to master or failure to master stress. Most studies of stress have in the past concentrated either on the acute emergency phase related to the adrenal medulla, or on the sustained reactions, seen as an illness, related to the adrenal cortex. The third phase concerned with the ability or failure to master the threats, whether internal or external, is crucial for the determination of "sickness" or "health". This ability to master stress is ego function.

The studies of A. Freud (19) and Erikson (15) are especially important in this regard.

In other studies of ours (28), we distinguished between the type of acute emergency reaction as the "style" or "basic disposition" of the personality and the ability to handle stress on a time continuum as "ego function". The psychological correlates of the "style" or "basic disposition" of the personality were only random in relation to "ego function"; the psychological correlates of "ego function" were only random in relation to the "style" or "basic disposition" of the personality. This suggested that two different aspects of personality were represented by these two phases of stress.

In this frame of reference, the type of adrenal medullary secretion during acute stress and its psychological correlates indicate the "style" of reaction. The factors relating to whether or not the reaction will become sustained lie elsewhere. In really understanding the problem of the mentally ill, we badly need intensive studies closely related to "ego function", both on a psychological and a physiological level. In our theoretical framework, the acute emergency reaction of subjects is predictive of the qualitative content, psychological and physiological, of a psychosis or psychosomatic illness, should one develop; proneness to develop such reactions is more closely related to the ability to handle stress on a time continuum ("ego function").

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BEHAVIOR OF THE SALAMANDER UNDER THE INFLUENCE OF LSD-25 AND FRENQUEL, AND ACCOMPANYING ELECTRICAL ACTIVITY OF BRAIN AND SPINAL CORD[1]

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INTRODUCTION

Recent studies of the behavior and electrical activity of the nervous system of the salamander under the influence of neuropharmacological agents indicate the suitableness of this animal for the investigation of fundamental problems involving the brain and spinal cord (4, 5, 6). Seizures with tonic and clonic phases can be induced, modified by commonly used anti-convulsant drugs, and the accompanying changes in electrical activity of the nervous system recorded with standard techniques. In view of the interesting yet complex effects of Frenquel and LSD-25 on human subjects as reported by Fabing (3), the single and combined action of these two drugs on the salamander was investigated with the hope that data obtained from a study of this relatively simple animal would yield clues to an understanding of the action of this drug on more intricate forms.

MATERIALS AND METHODS

About 60 male salamanders, the aquatic phase of *Triturus viridescens*, were used for the present study. Drugs were dissolved in 0.05 to 0.10 cc. of distilled water and injected into the abdominal cavity at the following optimum doses per gram of body weight: LSD-25 (D-lysergic acid diethylamide tartrate), 0.7 to 0.8 mg.; Frenquel (alpha-(4-piperidyl) benzhydrol hydrochloride), 0.3 mg. To investigate the effects of the drugs at various functional levels of the central nervous system the following behavioral tests were applied: 1) the withdrawal response, which is evoked by touching the tail and involves a spinal arc; 2) the righting response, which involves the 8th nerve and the vestibulo-spinal system; 3) the corneal reflex, which involves the 3rd, 5th, 7th cranial nerves, and associated structures; 4) the swimming and 5) the walking responses, which are a patterned automatic sequence of movements involving the striatum; 6) the visual response, in which the head and eyes undergo optokinetic nystagmus in following black and white stripes on a moving drum. This last test is a measure of attention and involves the 2nd cranial nerve, the optic tectum, the tecto-spinal and tecto-bulbar paths. These tests were applied every 15 minutes during the two hours following the injection of the drug, and every half hour for the subsequent 10 hours. For evaluating the responses, an arbitrary system was established in which "0" was normal and 1 to 6 referred to increasing degrees of deviation. These results are graphically summarized in figure 1.

A Grass model III-D, four channel electroencephalograph was used for recordings of electrical activity. Stainless steel electrodes were inserted into the skull to a depth of 1 mm. over the olfactory and tectal areas, and two hook electrodes were placed in the skin over the upper thoracic and lumbar segments of the spinal cord (fig. 2). Two channels were used for simultaneous recordings which are illustrated in figure 3.

OBSERVATIONS AND RESULTS

Effects of LSD-25. Within 5 to 15 minutes after the injection of LSD-25 the salamander, when placed in water, shows disturbances of equilibrium during which the animal slowly writhes, comes to rest on its side, back, or belly, and assumes statue-like postures representing some stage in standing or walking. These floating postures are interrupted by slow movements of trunk or limbs as if the salamander were attempting to maintain its balance. The trunk and limbs are not limp,

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[1] This investigation was supported by research grant, B-201, Division of Neurological Diseases and Blindness, Public Health Service. We are indebted to Sandoz Pharmaceuticals, Inc., for LSD-25, and to Wm. S. Merrel Co., for Frenquel.

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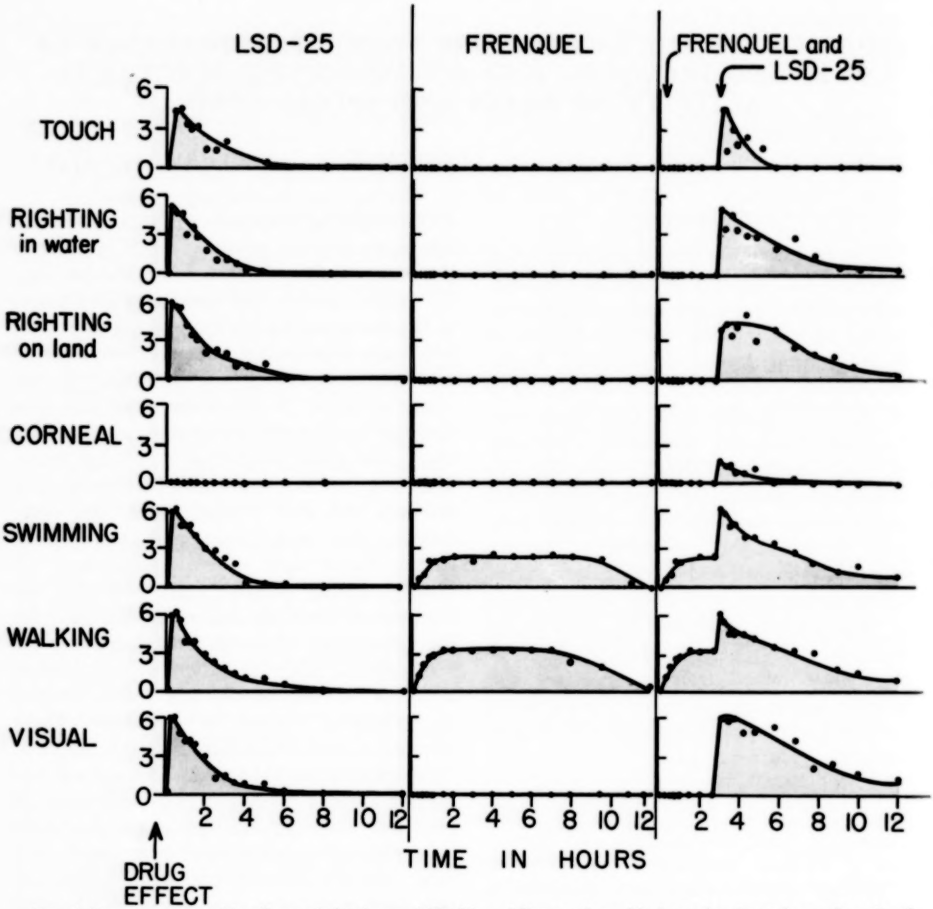

FIG. 1. Sensory-motor side effects of the drugs, LSD-25 and Frenquel used independently and together. On the vertical axis are plotted modifications of normal activity, in which 0 is regarded as normal and 6 as an extreme modification. Each dot represents the average of observations on 4 to 7 salamanders.

but have the firmness of soft wax, so that the animal allows itself to be moved passively, especially in water. During this phase of drug action, tactile stimuli applied to the tip of the tail are followed by ambiguous results, i.e., they may evoke a prompt escaping reaction as vigorous as that of an untreated animal, or a slow response delayed 5 to 10 seconds, or no response at all. The visual test is typically negative; nevertheless, electrodes applied to the optic area of the brain indicate that flashes of light on the eyes result in corresponding changes in the visual mechanism. A touch of the cornea is followed by a withdrawal of the eyeball. An examination of the peripheral circulation showed that the lumen of the blood vessels is normal with a typical flow of blood. These effects on external behavior become apparent 5 to 15 minutes after the injection of the drug, reach their peak in 15 to 30 minutes, and gradually disappear in 2 or 3 hours (fig. 1). Even at the same dosage, the intensity of the effects and their duration may vary somewhat from animal to animal. Generally the effects of the drug disappear by the following day or sooner; however, in some salamanders there is some stiffness in walking and a slower response to stimulation for one or two days after the use of LSD-25.

A few minutes after the injection of LSD-25 the electrical activity of both brain and spinal cord shows a brief drop in potential, but this is soon followed by the appearance of a strong and sustained increase in potential, especially in the spinal cord, even though the salamander appears quiet and motionless (fig. 3). These high potential waves consist predominantly of 18 to 22 per second waves, on which are superimposed some 30 to 40 per second waves of lower amplitude. The sustained electrical discharge lasts from 5 to 15 minutes and may be interrupted occasionally by movement artifacts. In about 30 minutes the electrical activity of both brain and spinal cord drops to a potential which is slightly lower than normal.

Effects of Frenquel. Within 30 to 60 minutes after the injection of Frenquel the salamanders show abnormalities in walking and swimming. Walking is marked by unsteadiness of gait and a limp in the forelegs. At times the weakness of the forelegs becomes so extreme that they are inadequate to sustain the weight of the head, and locomotion is accomplished mainly by a use of the hind limbs. In normal swimming the forelimbs are kept close to the trunk and point caudally; under the influence of Frenquel the forelimbs are extended somewhat laterally, and swimming movements are wobbly. These abnormalities in walking and swimming become more conspicuous as the Frenquel-treated animal is exercised. Some of the salamanders showed a slight, temporary, swelling and pinkness of the abdominal regions, yet the flow of blood in the peripheral vessels appeared normal. At a dose of 0.3 mg. per gram of body weight, the remaining neurological responses were typically unaffected (fig. 1). Frenquel reaches its peak effect on external behavior in about 3 hours and maintains it for about 3 hours more. There is a return to normal behavior in 12 to 24 hours.

At the time when Frenquel exerts its maximum effect on external behavior, the electrical activity of brain and spinal cord shows an extremely low amplitude, with dominant frequencies of 10 to 12 and 18 to 22 waves per second. Dosages over 0.4 mg. per gram intensify the effects described above and result in an extreme swelling of the abdominal region, circulatory disturbances, and death in a few days.

Effects of Frenquel followed by LSD-25. When LSD-25 was injected at the peak of Frenquel action, the salamanders still exhibited disturbances of equilibrium, statue-like postures, and slow writhing movements when in water. However, handling the salamanders indicated that the trunk lacked the firmness found in animals given only LSD-25. The electrical activity of the brain and spinal cord of a salamander receiving Frenquel, and later LSD-25, indicates that the LSD-25 may raise the low electrical potential found in salamanders receiving only Frenquel; however, LSD-25 does not evoke from the spinal cord the prolonged electrical discharge of high potential, typical of salamanders receiving only LSD-25. With the dosages and methods used in this investigation, Frenquel and LSD-25 mutually modify the effects of one another. When the drugs are used together, they exert a depressant effect on behavioral responses and produce a weakened condition which lasts 12 or more hours (fig. 2).

In determining optimum dosages of LSD-25 and Frenquel it was observed that different dosages may evoke quite different effects. This observation holds true especially for LSD-25 which seems to merit more thorough study.

Discussion

Electroencephalographic recordings indicate that the statue-like postures are accompanied by a sustained tonic discharge of high amplitude typically from the spinal cord, but occasionally involving the brain also. This prolonged tonic discharge does not achieve the severity and the extremely high amplitude with subsequent larval discharges and clonic components evoked by metrazol (5).

The very slow movements and statue-like postures of salamandeis while under the influence of LSD-25 were similar in many respects to those described for Siamese fighting fish (1); however, the salamander requires larger dosages than the fish to evoke these effects.

The fact that the electrical activity of the brain can show only slight changes while the spinal cord is undergoing intense and prolonged electrical discharges indicates that some of the effects of LSD-25 have a dependence on lower centers. These data seem to add further evidence to Bradley's (2) opinion that some of the effects of LSD-25 require mesencephalic or spinal connections. Even in the relatively high

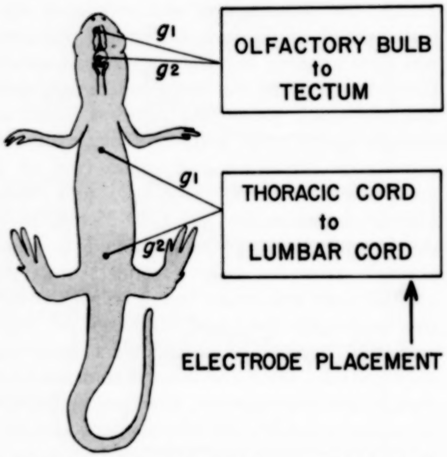

FIG. 2. Dorsal surface and exposed brain of the salamander, *Triturus viridescens*, and electrode placements used for bipolar recordings shown in figure 3.

doses used in this experiment the specific action of the drug is indicated by the retention of the corneal reflex during the peak of drug action (fig. 1).

In some respects the behavioral reactions of the salamander are only analogous to reactions of higher forms, especially of man. Yet the nervous systems of amphibians and mammals are fundamentally similar, and results obtained in the study of one form aid an interpretation of corresponding results in the other form. With this caution in mind attention is called to the irregular spacing of dots showing the response of the salamander to tactile stimulation while under the influence of LSD-25 (fig. 1). At this stage of drug action the response was unpredictable, often delayed, and sometimes absent. This type of reaction seems to indicate that LSD-25 causes some distortion in sensory perception and motor response, a condition which in man would cause loss of orientation, uncertain contact with reality, and apprehension. Furthermore, this distortion seems to take place not in the receptors themselves but in connector systems between afferent and efferent nerves. The salamander's response to the visual test while under LSD-25 was negative. During this phase of drug action electrodes placed alongside the tectum picked up electrical changes with every flash of light, indicating that the receptors in the eye were functioning. Since the animal could walk and move at this time, the inhibition or distortion likely had its location at connections in the central nervous system. Purpura (7) described a differential excitatory and inhibitory action of LSD-25 in its effect on the cat's brain.

At the dose used in this study, Frenquel seems to leave the salamander in a state of relaxed alertness. Relaxation is indicated by the very low electrical potential of both brain and cord and the relative infrequency of muscle potentials; the alertness is indicated

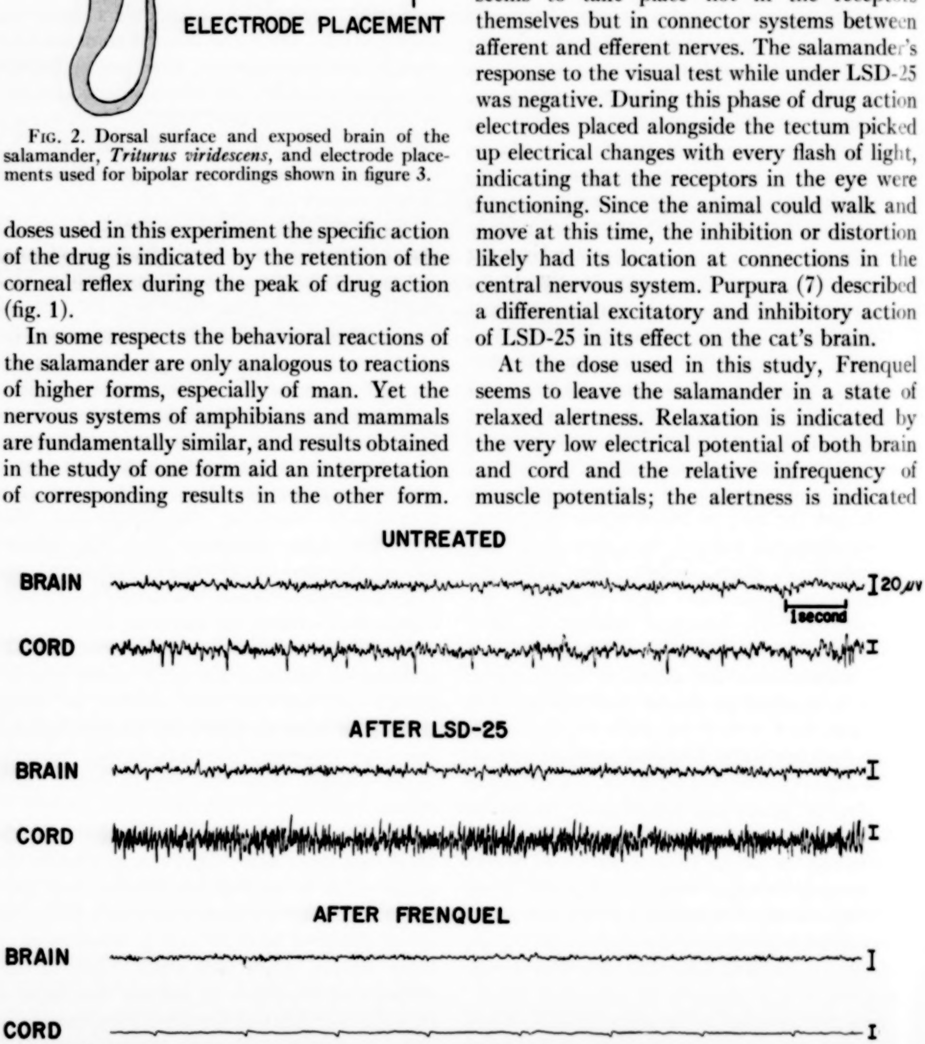

FIG. 3. Selected typical records of electrical activity of brain and spinal cord of untreated salamanders, and of those which received LSD-25 about 10 minutes before, and Frenquel 3 hours before.

by ability of the salamander to respond promptly to tactile stimulation unless the animal is exercised to the point of fatigue. This conclusion seems to agree with Fabing's (3) comment that Frenquel is not a central excitant.

Although a combined use of LSD-25 and Frenquel at the doses employed in this study leaves the salamander in a weakened and depressed condition, it is likely that with more careful study a dose of the two drugs could be found which leaves the animal in a more active and alert condition.

SUMMARY

1. In the salamander, LSD-25 depresses the behavioral responses of touch, righting, swimming, walking, and vision, but the corneal response remains. During the peak of drug action the salamander assumes statue-like postures, and the electrical activity of the spinal cord shows a sustained discharge of waves of high frequency and amplitude.

2. Frenquel modifies the behavior of the salamander by producing unsteadiness of gait, weakness of forelimbs, and a wobbly method of swimming. During the height of Frenquel action the electrical activity of both brain and spinal cord shows waves of very low amplitude.

3. With the dosages and methods used in this investigation, Frenquel and LSD-25 in some measure mutually modify the effects of one another. When the drugs are used together, they exert a depressant effect on behavioral responses and produce a weakened condition.

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STUDIES ON MESCALINE

VII: The Role of Anxiety in the Mescaline-Induced State and Its Influence on the Therapeutic Result

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Clinical observation during the combined use of mescaline and chlorpromazine as therapeutic agents in a psychodynamic frame of reference suggested that anxiety played an important role in the genesis of the mescaline-induced state, and was one of the determinants of the end result (1). Anxiety appeared to be the "motor" driving the psychic state evoked by mescaline. When the drug gave rise to an acute unbearable and intolerable state of anxiety, symptoms developed rapidly. By freely associating thoughts and discharging feelings, patients became aware of hitherto repressed elements in their past life. The injection of chlorpromazine rapidly blocked the mescaline-induced state, leading to tranquility, lethargy and somnolence (2). Afterwards it was possible to review retrospectively the newly found material. On the other hand, when anxiety was lacking following the injection of mescaline, dullness, apathy and few symptoms were observed. There was a marked paucity of inner experiences, and few freely associated thoughts were available for analysis.

To what extent, if any, does anxiety influence the therapeutic action of mescaline? Is anxiety at all necessary? If the patient could experience the mescaline-induced state without the all pervasive anxiety, could the end result thereby be facilitated and enhanced?

It was believed that premedication with various compounds capable of blocking the action of mescaline might selectively inhibit the tension-anxiety component. In this setting the role of anxiety in symptom formation and therapy could be studied.

MATERIALS AND METHODS

Twenty-three female and 19 male patients, ranging in age from 16 to 42 years, were studied (table 1); 35 were schizophrenic (table 2). The interval between admission and treatment was 10 days or less in 24 patients (table 3).

Either chlorpromazine hydrochloride (50 mg.), promethazine hydrochloride (50 mg.), diethazine (250 mg.), or saline (2 cc.) was used as premedication (table 4). After initial trials with promethazine hydrochloride in six patients, the rest of the study was done blind. Neither the patient, ward personnel nor the physician was aware of the premedication used. The following procedure was used: Patients were selected at random on the day of admission, without prior knowledge of diagnosis, clinical condition or previous treatment. Initial data were secured at the preliminary interview. The premedication was given by intramuscular injection one-half hour before mescaline. One-half gram of mescaline sulfate dissolved in 20 cc. of physiologic saline was then injected intravenously. The patient was asked to freely associate his thoughts and express his feelings. After 45–60 minutes, either chlorpromazine (100 mg.) or saline was injected to terminate the treatment period. The patient was interviewed in the afternoon and on the following day. The code for each patient was revealed and the data assembled after the clinical results had been assessed and the study terminated.

RESULTS

1) *Premedication with either chlorpromazine, diethazine or promethazine.* Before the injection of mescaline, many patients who had received either of the phenothiazine compounds lay quietly on the bed. They responded to questions slowly, were lethargic and frequently said, "I'm sleepy." The initial symptoms of nausea, retching and vomiting were absent in almost all. The desire to urinate and to defecate, so often expressed immediately following the injection of mescaline, was rare. While the anxiety complex (tension, anxiety, panic, uneasiness and restlessness) was present at times, it was quantitatively decreased when compared to patients without premedication. Marked passivity, lethargy and unresponsiveness were most frequently seen. The various

symptoms produced by mescaline appeared without any particular pattern and were most often devoid of their affective charge. There was little incentive or desire to freely associate. Many of the patients stated repeatedly in a fatigued stereotyped fashion, "I have nothing to say." A striking inertness of the body paralleled the psychic inertia. Sexual feelings, either symbolic or verbalized directly, were infrequently observed.

An unusual state developed in five of 13 patients receiving diethazine before mescaline. These patients were extremely tense, anxious, restless, shouted, cried, gesticulated, complained of muscular weakness, and often staggered about the room. They lay on the floor and assumed bizarre postures on their hands and knees. They said their experiences were "indescribable". A panic state developed which was qualitatively different from that seen with mescaline alone. Intense fear and the appearance of "being in agony", or "terribly frightened", differentiated the former from the latter. Almost all of the patients receiving diethazine had great difficulty in verbalizing their feelings or thoughts. They seemed to be attempting to speak but were unsuccessful. The words, "no answer", "quiet", "sleepy", or "mute", were noted in their protocols.

Case report. A 26-year-old white schizophrenic male received 250 mg. of diethazine, followed one-half hour later by 0.5 grams of mescaline. Eight minutes after the latter injection was terminated, he said, "I'm suffocating. I see purple flashes. I didn't know that I was going." He got up; walked and staggered around the room; fell to his hands and knees; and clutched his throat. Thirteen minutes after the injection he was noted as being in an acute panic state, gesticulating and shouting, "I wanna do something right but I can't. They're killing me. What have I done wrong with my life?" He clutched his throat and screamed, "I hate everybody. What is all this? Oh, my God, it'll kill me." He was asked to elaborate on the meaning of these various actions and statements, but there was no reply. One hour after the injection of mescaline he was asked to describe his feelings. "It's indescribable horror. It comes and it goes. Horrors, horrors, horrors." Three minutes after the injection of chlorpromazine he was asked what had happened. He replied, "I can't describe it. It's indescribable."

TABLE 1

Age	No. of Patients
yrs.	
16–19	2
20–29	20
30–39	18
40–42	2

TABLE 2.—DIAGNOSES

Dementia praecox (all types)	35
Psychoneurosis	3
Manic depressive, depressed	2
Psychosis with psychopathic personality	1
Psychosis due to alcohol	1

TABLE 3.—TIME INTERVAL BETWEEN ADMISSION AND TREATMENT

Days		
1–5	—	12
6–10	—	12
11–19	—	7
20–30	—	5
>30	—	6

TABLE 4

Treatment Technique	No. of Patients
Diethazine-mescaline-chlorpromazine	13
Saline-mescaline-chlorpromazine	10
Promethazine-mescaline-chlorpromazine	9
Chlorpromazine-mescaline-chlorpromazine	5
Saline-mescaline-saline	5

2) The patients who received saline-mescaline-chlorpromazine or saline-mescaline-saline responded in a manner already described (1). Four of the five patients who received saline-mescaline-saline required intramuscular chlorpromazine after the procedure was terminated. Their agitation and restlessness were so severe that they disturbed other patients on the ward.

Four patients showed a complete remission of symptoms; eight patients showed some improvement; while the other 30 were unchanged following the treatment outlined above. Three of the four patients in a complete remission had been premedicated with promethazine and one with chlorpromazine. Of the eight patients who improved, one received promethazine, one chlorpromazine, two diethazine, and four saline before mescaline. None of the patients who received the saline-mescaline-saline combination showed any amelioration of their clinical condition.

DISCUSSION

The patients' response to intravenous mescaline with the usual mescaline-chlorpromazine technique followed a regular sequence. The central action of mescaline in some unknown way placed the individual in a set of intense anxiety that mounted in crescendo with each minute. This feeling was aimless or directed to a specific object. Initially it was without intellectual value and expressed purely on an emotional level. As the anxiety rose, the individual felt terrorized and in the grip of the unknown. He would then frequently grasp the physician's or nurse's hand and beg not to be left alone. Within 20–30 minutes, various symptoms began to appear. At this point, the therapeutic value of the procedure became apparent. By freely associating to these symptoms, conflict laden significant past memories and events were relived in a setting of intense emotion. As these feelings were discharged, the anxiety decreased.

The above train of events was sharply modified when premedication prevented anxiety formation to any appreciable degree. The patient was already drowsy, lethargic and dull before the mescaline was injected. While under the effects of the drug, the intensity of various symptoms was quantitatively decreased. The "motor" did not seem to be functioning. The treatment periods were poorly productive with little material available for free association. Spontaneity was lacking, and the sessions were ones of question and answer.

It is difficult to explain the curious action of the diethazine-mescaline combination. Diethazine alone will only produce some drowsiness. Large doses, such as those used in this study, have been noted to produce muscular atony with weakness in patients suffering from Parkinson's disease (4). The "agony and terror" may result from the welling up of unconscious conflicts unable to find a motor discharge. The combination of muscular weakness, staggering gait and difficulty in verbalization was noted only in those patients receiving diethazine-mescaline.

It was not possible to draw any conclusions concerning the relative blocking effect of the various agents used. The numbers in each group were too small. In studies dealing with the action of pharmacologic agents on behavior, one must take into account the marked variability from patient to patient. The results are only meaningful if large numbers of patients are studied and the investigation is done blind.

Freud (3) said that "all symptom formation would be brought about solely and in order to avoid anxiety . . . so that anxiety would be the fundamental phenomenon." Symptoms are in reality only a mirror of the unconscious and, as such, represent the external symbolization of inner conflict. They become in this manner peripheral stimuli and assume meaning in conformance with past experiences. As the patient responds to these stimuli, additional anxiety is generated with added symptom formation. The process continues, assuming the character of a reverberating circuit, until interrupted in some way—in these cases with chlorpromazine. The absence of anxiety, on the other hand, leads to an inner paralysis and is reflected outwardly by silence. When the anxiety evoked by mescaline is inhibited, symptoms are frequently lacking, and the therapeutic process is at a standstill.

Use of the various phenothiazine compounds as premedication suggests that the sequence—anxiety-symptom formation-free association-recall with awareness of unconscious conflict and discharge of feelings—is essential to the therapeutic process underlying the mescaline-chlorpromazine technique.

SUMMARY AND CONCLUSIONS

1. Forty-two male and female patients were studied with the mescaline-chlorpromazine technique following premedication with either diethazine, promethazine, chlorpromazine or saline.

2. Anxiety and symptom formation were significantly reduced when either chlorpromazine, diethazine or promethazine was used before mescaline.

3. Patients receiving diethazine before mescaline had great difficulty in verbalizing their feelings or thoughts. Five of 13 patients developed a state featured by muscular weak-

ness, staggering gait, difficulty in verbalization and acute panic.

4. Therapeutic results were poor where the phenothiazine compounds were used as premedication.

5. The role of anxiety in symptom formation and therapy with mescaline-chlorpromazine has been discussed.

I am grateful to the Smith, Kline & French Laboratories, Philadelphia, Pa., who, through Mr. William E. Kirsch, Research Associate, have provided continued support. Generous supplies of chlorpromazine ("Thorazine" SKF) and diethazine ("Diparcol" R.P.) were made available for study.

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THE EFFECT OF ELECTROCONVULSIONS, INSULIN COMAS AND CERTAIN CHEMICAL AGENTS ON FIXATIONS IN THE RAT[1]

ODDIST D. MURPHREE[2] AND JOHN E. PETERS[3]

Stereotyped patterns of behavior are an important element in most forms of mental illness. It may be that more suitable, more varied patterns cannot occur partly because of the domination of responses which, though maladaptive, have become deeply habitual with the passage of time, with practice, and with a high level of emotional participation.

Stereotyped "maladaptive" habits or "fixations" can be established in the rat. We define fixation in this experiment as an unvarying, maladaptive behavior pattern which is developed in response to a no-solution problem under conditions of stress, and which persists even when the problem is made solvable. This fixation is considered by us to resemble, to some degree, rigid maladaptive behavior in human beings. We hoped to throw some light on this process by studying the effects of various agents on the rat fixation, beginning with those agents whose effects in the human have been more thoroughly studied. Agents used were electroconvulsions (ECT), insulin comas (ICT), alcohol, chlorpromazine, reserpine, and d-lysergic acid-25 (LSD). The work with the latter four drugs, while only exploratory, was felt to be worth including in this report for the use of other investigators.

Assuming that varying intensities of emotion go into the making and maintaining of a habit, and that a fixation is merely an unusually strong habit, treatment could be aimed at mitigating or obliterating the memory component or the emotional component of the behavior pattern. And different agents could operate in different or in overlapping ways to bring about a change. A permanent or temporary breaking up of memory associations might allow new patterns to be formed, providing that the ability to acquire new learning was not disproportionately impaired. A reduction in fear or anxiety could put an animal in a better position to notice the cues which would lead to adaptive decisions at decision-points. The present research was designed to test certain agents as to their ability to impair fixations; their ability to facilitate the acquisition of adaptive behavior was left to later research.

The rationale for the inclusion of ECT, ICT, chlorpromazine, and reserpine in this study needs no special comment. Alcohol was included because of our common knowledge of its effects—as a kind of comparison. LSD was included because of the possibility that its dissociating ability might break up well-established patterns and allow new ones to be formed.

METHOD

Thirty-nine male and 21 female Sprague-Dawley rats were run after 24-hour water deprivation in a simple T-maze for 10 trials per day, three days a week. They were allowed Purina Dog Chow ad libitum, and water ad libitum except as stated above. During these trials, rats were randomly rewarded with water or punished with electricity (approximately 50 volts) in the arms of the T so that there could be no solution to the problem, other than removal from the T by hand after the reward or punishment. The trunk of the T was always electrified (approximately 50 volts). The animals were run for 300 trials which was 50 trials after 100 per cent of the animals had become invariable in their choice as to the arm of the T. For the 100 trials just prior to that point, 19 rats made changes; but these were very few as compared with frequency of "correct" (fixated) runs. Thus all rats were eventually fixated, and none discarded. Results during the experiments showed that late fixators were no more likely to lose fixations than early fixators. The problem was not made soluble until the actual experiments with the agents were begun. After the fixations were established, the rats were divided into experimental and control groups. The control groups rested while the experimental rats underwent treatment.

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[1] Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the results of this study and do not necessarily reflect the opinion or policy of the Veterans Administration.

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The ECT group (17 rats, 3 of which died of broken backs as a result of the treatment) received 18 convulsive treatments on 18 consecutive days and was tested for persistence of fixations along with controls (8 rats) after 3, 6, 12, 15, and 18 convulsions. They were again tested for retention after intervals of 3, 9, 36, and 67 days. ECT was administered with a commonly used apparatus: Medcraft Model B-24, which delivers a sine wave, 60-cycle alternating current. A variac was interposed between source of current and apparatus such that settings as low as 57 volts were utilized. The usual setting was 65 volts for 0.2 or 0.3 seconds.

The ICT group (17 rats, 3 of which died in insulin coma) received 18 insulin comas on 18 consecutive days and was tested along with controls (11 rats) after 4, 8, 12, and 18 comas. Insulin doses were administered subcutaneously and ranged from 4 to 10 units per rat. Rats were fasted for 12 hours prior to insulin injection. Comas were terminated after about 2 hours with multiple subcutaneous injections of 10 per cent dextrose (usually totaling 6 cc.).

The rats who received drugs and who showed no changes were used again in the ECT and ICT experiments, care being taken to distribute drug rats between treated and controls of the ECT and ICT experiments. Various dosage levels were tried, and the dosage which produced a marked, observable effect was the one finally used. All drugs were given subcutaneously unless otherwise stated. Ethyl alcohol: 2 cc. of a 50% solution were injected subcutaneously plus 4 cc. orally of a 20% solution, totaling 1.8 cc. pure alcohol. These rats were tested 1½ hours later when they had difficulty standing. Chlorpromazine: Average of 3.75 mg. per rat (12.5 mg./kg.). Testing for presence of fixations was done at 1, 3, and 6 hours subsequent to injection, and again 2 days later. Reserpine: average of 0.15 mg. per rat (0.5 mg./kg.). Testing was done 8 hours later. LSD: 4 micrograms per rat (13 micrograms/kg.) and on another occasion 12 micrograms per rat (40 micrograms/kg.). Testing was done 1½ hours after injections.

In order to determine whether there was any learning deficit due to ECT or ICT, these rats were run in a modified Stone 14 choice-point multiple T-maze until all rats had approached mastery of the maze.

Discussion of Method

Most fixation studies with rats have used the Lashley jumping stand, which is the method pioneered by Maier (11). The stand is placed before two windows in which may be placed appropriate light and dark covers which serve as signals. The rats may become invariable in their choice either of a window with one intensity of light behind it or may establish a right or left position fixation. With this method the rat makes his decision while driven by hunger, thirst, or pain (or combinations) and before he has got into action. His decision involves two alternatives, one of which may lead to relief of drive, and the other to a bump on the head or body and falling into a net.

We had hoped that the T-maze would offer a simpler, quicker method of fixation, but the relative merits of the two methods were not elucidated in this research. One point of difference is that the rat is already in rapid motion down the trunk of the T when he makes his right or left decision—which distance (and action) could allow for some dissipation of fright before the decision point is reached. The work of Obias and Stone (13) suggests that the closer the impingement of a stressful situation on the decision point, the less adaptive the decision is. Another difference is that our rats in the T-maze situation were not so dependent on the cues of vision in developing fixations, whereas with the jumping stand method they are forced to use their eyes. This is a much less natural avenue for the laboratory rat, and consequently might have put the rat under greater stress or another kind of stress than produced by our method. The terminal escape is similar for both methods: after falling into the net the rat is returned by hand to his box; in our method, after he has been shocked or rewarded with water in the arm of the T, he is lifted out and placed in his box.

Another factor which could make for differences in fixation: other methods mass trials, 10 per day every day, whereas we used 10 trials on two or three days a week. Neet

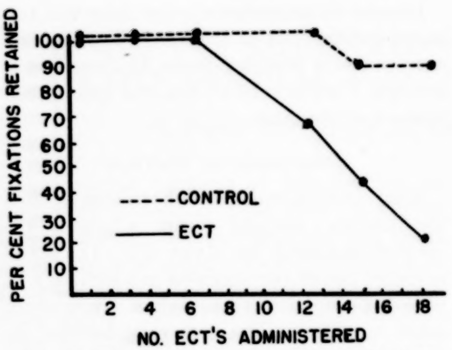

FIG. 1. The reduction of fixations as ECT administrations progress.

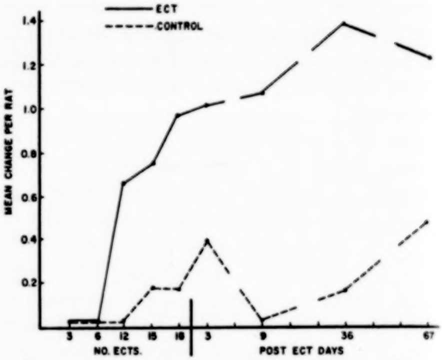

FIG. 2. Variability produced by ECT on fixated rats.

and Feldman (12) eliminated those rats which had not fixated by 160 trials, whereas we carried all rats to the point of fixation.

One important shortcoming of the rat fixation as a tool is that its persistence depends on certain external stresses to keep it in operation. It is not "built-in", self-propelled as so much human pathological behavior appears to be. And those very external stresses may constantly counteract the mitigating effects of whatever treatment agent is being investigated.

RESULTS

The only agent which decisively affected the fixations was ECT. The per cent of rats changing direction after different numbers of ECTs is shown in figure 1. The retention tests were run on the day after ECT (two or three trials). By the day after the 18th ECT, 11 out of 14 experimental rats and one control had altered direction one or more times. Using Fisher's Exact Test, this difference is reliable at the 1 per cent level of confidence. Three days later a retention test showed that one more experimental rat and one more control had changed. Thirty-six days later two more ECT rats and one more control had shown variability. In the period from the 18th ECT to 67 days later, one experimental rat and three control rats made no changes; one experimental and one control made one change; one experimental and four controls made two changes; four experimentals made four changes; three experimentals made five changes; one experimental made six changes; one experimental made seven changes; and two experimentals made nine changes—out of a total of 16 test trials. As a measure of strength of fixation all trials after the 18th ECT for all rats were totaled: in the experimental group, out of 145 trials 57 were opposite to the fixation (39%); in the control group, out of 82 trials only 6 were opposite to the fixation (7.3%).

Figure 2 shows the mean changes per rat per experimental day. In this graph a change means going opposite to the immediately preceding trial. This shows clearly the greater variability of the experimental as compared with the control groups; that is, once having changed direction the experimental rats tended to continue to change; whereas the controls who changed at all tended to revert to fixation and remain so.

Eighteen insulin comas had no effect on the fixations. No rat of the 14 who successfully completed the 18 treatments changed his fixation, but one control did change once.

Six of 14 rats injected with chlorpromazine changed away from their fixation while under the obvious influence of the drug, and two of their controls changed. When tested two days later, however, all these rats had reverted to their fixated responses. This result suggests that sustained treatments with chlorpromazine should be tried and physical guidance added to see if the drug allows for a giving up of the fixation in favor of the adaptive alternative.

Reserpine and alcohol experiments yielded completely negative results. A very few rats changed while under the influence of the two different doses of LSD, but there was no

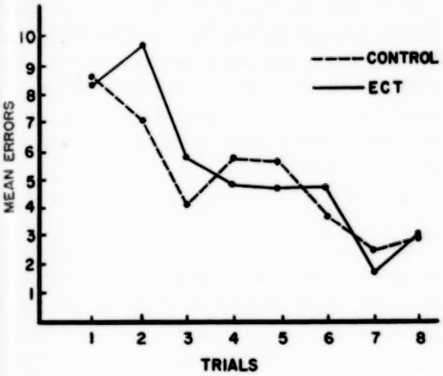

Fig. 3. The effect of ECT on complex maze learning.

significant difference between these and the controls. These few experiments do not negate the possibility that more treatments plus guidance would facilitate the breaking of fixations and learning the adaptive path.

Comparisons of the ECT and ICT groups with their controls on the 14 choice-point maze disclosed no gross decrement in learning proficiency though experimental rats showed a few more errors than their controls.

Discussion

In these experiments ECT was effective in removing a strong, acquired pattern of behavior and so allowed a different pattern to occur. The different pattern was that of random choice of direction. In that the native pattern is that of random alternation, the fixation and the random pattern could be considered as competing, though not in quite the same sense as the competition between an old habit of going right and new one of going left. As compared with the native pattern of random alternation, the fixation was a relatively new, but highly practiced, stressfully developed pattern. If the random pattern had appeared only in the first few days after the last ECT, simple confusion (whatever that is) might account for the results; however, randomness continued for at least nine weeks. This indicates that the fixated pattern was greatly weakened or obliterated. However, the ability of the ECT rats to learn the 14 choice-point maze was only slightly impaired.

Palmer (14) also found that ECT (25 treatments) increased variability of response in rats which had been fixated in a double alternation maze, but that on massed retesting the old fixations tended to return and the rats did not acquire more efficient patterns.

Neet and Feldman (12) using a Lashley jumping apparatus for forming fixations, concluded that 25 ECTs were not effective in causing their rats to abandon fixations and learn a solvable problem. They state that a 25-day series of ECT "had no major effect on the stability of the rats fixated responses." Actually 7 out of their 9 rats showed variable behavior, but apparently during the 200 post-shock trials (massed at 10 per day) the fixations reasserted themselves. This may account for the difference in our results in that we avoided massed trials and tested with usually 3 trials at intervals of 1, 3, 9, 36, and 67 days post-shock. The random behavior was decidedly present two months later, whereas the control rats continued at a high level of fixation. Other possible differences could derive from the different methods of fixation used. Moreover our testing days were spaced so far apart that it would be unlikely that even an unfixated rat could develop an adequate response to the problem now made solvable; so that our results show only a loss of fixation and do not indicate whether ECT rats would make an adaptive response in the same situation less well or better than controls.

The present work indicates that ECT impairs memory, a fact which is well known. Recency (5, 18), degree of practice (3), and complexity of task (4, 14, 17) are important determinants of memory which are differentially susceptible to ECT. Previous work of one of us (15), Hunt and Brady (2, 9), Gellhorn (7), and observations on clinical cases (1) suggest that the therapeutic effect of ECT is due more to its action upon the emotional and autonomic correlates of learned behavior than upon the cognitive or symbolic elements. If the latter were the case, the efficacy of ECT would depend very much upon the degree of amnesia produced, and this is not true in clinical work. In most animal work the effect on more or less normal learning and memory has been studied; yet it may be that the pertinent effect is on specific pathological processes of brain functioning rather than upon normal processes. If such is the case, the studies on relatively normal animals are somewhat off the point.

Fabing (6) has postulated an interesting theory for the effect of ECT on memory. He suggests that nerve nets which are in a state of high excitation are driven to the point of exhaustion by ECTs producing a state of inhibition which is more profound than that of the adjacent nerve nets which had not been previously overworked. He further suggests that this inhibited state may be a Pavlovian ultraparadoxical phase of cortical activity; i.e., that which had been highly excited becomes deeply inhibited and *vice versa*, and that these previously more active nerve nets take longer to recover than less active ones. Therefore, memories carrying a heavy emotional "charge" would be forgotten and trivia more easily remembered.

There is some evidence that ECT selectively impairs the process of inhibition more easily than that of excitation (8, 10), yet how is this process to be separated from recency (5) since generally a process is excitatory before it can be made inhibitory?

It is well known among clinicians that insulin comas have relatively little impairing effect on memory. However, Riess and Berman (16), experimenting upon maze learning in rats, found that one insulin coma (or convulsion) did impair the more recent, the less practiced, and the more complex patterns. Our fixations were "old" by comparison, were highly practiced, and were very simple, which could account for the fact that our fixations were not affected at all by 18 comas. Since Riess gave larger doses of insulin, starved rats for 24 hours, terminated comas with small doses of glucose, and subjected rats to tests "after a recovery period" (length of time not stated), one wonders whether they might not still have been hypoglycemic at the time of testing.

Though ICT and ECT affect memory differently and may bring about results by different machanisms, still both methods have their greatest efficacy in the treatment of acute psychoses and not in the treatment of the deeply habitual processes of chronic psychoses. This supports in some measure the position that studies on learning, memory, and fixations have pertinence to the problem of maladaptive behavior and mental illness. However, it may be that ICT and ECT are therapeutic because of their action upon certain as yet undetermined pathological, neurophysiological or neurochemical processes which are at their height in the acute stage and which happen to share with learning and memory some common laws.

SUMMARY

Albino rats were run in a T-maze with random reward and punishment (no-solution problem) until they became fixated in a left or right direction. ECT and insulin comas were administered to different groups to see if the fixations were altered. ECT decisively reduced the fixations, but insulin comas had no effect. The effects of chlorpromazine, reserpine, d-lysergic acid-25, and ethyl alcohol were studied on an exploratory basis. Chlorpromazine caused a temporary change; the others had no effect. More extensive experimentation on the relative ability of these agents to facilitate adaptive responses is needed.

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THE DERMATOLOGIC AND SYSTEMIC MANIFESTATIONS OF CHLORPROMAZINE HYPERSENSITIVITY

Their Clinical Significance and Management[1]

FRANK J. AYD, JR., M.D.

The administration of Thorazine (chlorpromazine) in large doses for prolonged periods has caused physiologic, endocrine, and neurologic responses that merit serious study; it has also caused toxic reactions which forbid its indiscriminate use.

Clinical experience has shown that drugs can produce effects other than the normal therapeutic effect. In most cases these side reactions are attributed to individual hypersensitivity to the drug although the mechanisms that underlie this hypersensitivity are not fully understood.

Immunochemists believe that in the chemical structure of a new drug may be found a clue to the riddle of whether or not the drug will sensitize. They have discovered that certain chemical compounds are antigenic, especially compounds with a pyrimidine nucleus and compounds with a benzene ring as a nucleus to which a labile NH_2 group or chlorine atom is attached, particularly if they contain acid groups such as sulfonic or arsenic acid (1).

Thorazine is a phenothiazine derivative. Since its chemical structure contains two benzamine rings with a chlorine atom in position 2, it is understandable that this drug causes dermatologic and systemic manifestations of drug sensitivity.

DERMATOLOGIC REACTIONS

The skin reactions to Thorazine, which are the most common allergic reactions to this drug, are as follows:

1) *Exanthematic eruptions.* These may be erythematous with macular and papular eruptions and scarlatiniform eruptions. The exanthemata, as well as the other forms of skin reaction to Thorazine, occur within the first four weeks of treatment and may be accompanied by a transient fever and pruritus of varying intensity. They may last from 1 to 5 days and may disappear even when Thorazine is continued.

2) *Urticaria.* This may vary from small elevated patches to giant hives and large areas of circumscribed angioedema. This latter reaction most often involves the lips. Pruritus may be intense. The urticaria subsides in a few days, whether or not Thorazine is continued.

3) *Contact dermatitis.* This occurs when this drug is handled without precaution. It begins on the hands with an eczematous lesion followed by edema, redness, vesicles, infiltration, fissuration and desquamation. It may spread over the arms, neck and face. Positive patch tests definitely prove Thorazine responsible for the contact dermatitis (12).

4) *Photosensitivity.* This may vary from mild to severe erythema with edema of the surface of those areas exposed to the sun. Rarely it may be manifested by a papular polymorphic light eruption. It is a seasonal problem, occurring from May to October, when most people are exposed to the summer sun. Because of the intense itching and discomfort that appear early in photosensitive patients, few of them are exposed to the sun long enough for the burn to proceed to vesiculation. Some patients remain photosensitive as long as they take Thorazine, but most become desensitized by repeated limited exposure to the sun.

There is no relationship between photosensitivity and the dosage of Thorazine. The incidence of this side effect is difficult to predict because many potentially photosensitive patients are not exposed to the sun. Of 200 ambulatory patients treated by the author, 12 per cent were photosensitive.

The mechanisms underlying Thorazine photosensitivity are unknown. Cohen and Nash found that topical application of this drug and its oxidized form do not result in photosensitization, but oral or parenteral intake of this drug may (3).

5) *Erythema multiforme and generalized ex-*

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[1] Thorazine generously supplied by Smith, Kline & French Laboratories, Philadelphia, Pennsylvania.

foliative dermatitis. These occur infrequently in patients taking Thorazine. Although no cases have been reported, Thorazine could cause bullous eruptions, purpura simplex and fixed drug eruptions.

Clinical significance and management

Patients with Thorazine skin reactions usually are not ill although Moyer mentions a a patient with a generalized exfoliative dermatitis who was seriously ill with a high fever and delirium (8). It is seldom necessary to discontinue Thorazine because of a skin reaction. However, if the drug is withdrawn, it may be resumed safely after the dermatitis clears.

Antihistaminics satisfactorily relieve the pruritus that accompanies Thorazine skin reactions. Large doses may be required for patients with giant hives and angioedema. Cortisone may be necessary for the occasional severe dermatitis.

Photosensitivity is the most uncomfortable skin reaction to Thorazine. Ambulatory patients should be advised of this potential side effect and warned not to sun bathe. The burning sensation and the itching resulting from it may be severe. Antihistaminics relieve this and should be prescribed for the photosensitive patient until he is desensitized.

SYSTEMIC REACTIONS

Although systemic reactions to Thorazine are infrequent compared to the large variety of skin eruptions caused by this drug, they deserve special attention because they are potentially dangerous and may result in death. The systemic reactions to Thorazine have been limited to the following.

Hepatitis

1.4 per cent of the patients receiving Thorazine develop jaundice (4). This has been precipitated in almost all cases by small doses of the drug (75 mg. to 200 mg. daily) within the first month of treatment. In a few instances Thorazine was stopped after a brief period of treatment and jaundice appeared 1 to 2 weeks later. The usual prodromal symptoms of jaundice may or may not occur. It may be preceded by a transitory eosinophilia.

Thorazine jaundice is obstructive in type. Since it has occurred most often in patients over 40, the mistaking of it for jaundice due to a neoplasm of the head of the pancreas caused futile exploratory laparotomies. This may be avoided if the doctor is patient, since Thorazine jaundice almost always subsides within 4 weeks. The longest period of Thorazine jaundice on record is 7 months.

Clinical significance and management. Most clinicians discontinue Thorazine when jaundice appears; others do not, and the jaundice clears anyway. It is safe to re-treat patients, even with large doses, after jaundice has subsided, as is illustrated by the following case:

> Thorazine, 25 mg., t.i.d., was prescribed for a 48-year-old woman. Jaundice appeared 20 days later. Medication was stopped, and within 10 days the jaundice cleared. Thorazine was resumed. For 6 months this patient took as much as 1,000 mg. daily, but jaundice did not recur.

Thorazine is not hepatotoxic although Boardman has reported a fatal jaundice in which the autposy diagnosis was toxic hepatitis (2). Liver biopsy specimens from patients with jaundice have revealed cholestasis in the liver parenchyma. After recovery from the jaundice, liver biopsies and liver function tests have not disclosed residual liver damage.

Thorazine jaundice is probably an allergic reaction in certain predisposed individuals. This is based on the following facts:

1) The relatively low incidence of jaundice in view of the extensive use of Thorazine.

2) The small dose of this drug precipitating jaundice when other patients have taken large doses (up to 4,000 mg. daily) with immunity.

3) The occasional latent period between termination of therapy and the appearance of jaundice.

4) The occurrence of other expressions of Thorazine hypersensitivity, particularly skin eruptions and photosensitivity in the same patient.

5) The safe administration of this drug to many patients with liver damage.

6) Experiments showing that Thorazine is not hepatotoxic.

7) The re-treatment of patients, almost always without the recurrence of jaundice.

Whether or not Thorazine should be stopped when jaundice appears is a matter of the doctor's discretion. For most patients special treatment is unnecessary. I have hospitalized only one patient with jaundice. This was the first patient to develop jaundice when I first began to use Thorazine. Since then, I have treated my jaundiced patients on an ambulatory basis without any adverse consequences. Compared with the reports in the literature my patients recovered as rapidly as the patients who were hospitalized and placed on special diets, i.v. fluids, and medication.

Blood dyscrasias

Thorazine is a recent addition to the growing list of drugs capable of inducing agranulocytosis. This expression of Thorazine hypersensitivity has been rare. The literature contains only six cases of agranulocytosis due to this drug (5, 6, 7, 9, 10, 11). Since three of these patients died, this side reaction is serious.

The early reports of Thorazine agranulocytosis focused attention on the possibility of this complication and the need for prompt detection and treatment if a fatality is to be avoided. I know of 11 unreported cases of Thorazine agranulocytosis, including two of my private patients. Of this group, three died; the others recovered after treatment with antibiotics, ACTH, and transfusions. This reduced mortality rate emphasizes the value of prompt detection and treatment of agranulocytosis.

These are the important clinical facts about Thorazine agranulocytosis:

1) It is most probably an allergic phenomenon.

2) It may have a sudden onset or it may follow a slow progressive leukopenia.

3) The only warning of agranulocytosis may be the development of extreme malaise or weakness. In some instances the onset is silent; in others it is accompanied by chill, fever, diarrhea, prostration or signs of secondary infection of the mucous membranes.

4) It appears after the first month of treatment usually between the 40th and 70th day. In one of my patients, a 14-year-old boy, granulocytopenia was detected on the 121st treatment day.

5) It occurred most often in women.

6) Practically all patients were over 40 years of age.

Clinical significance and management. Agranulocytosis is the most hazardous complication of Thorazine therapy. Its seriousness can be reduced by early detection and prompt treatment. It is incumbent on the physician who prescribes Thorazine to instruct patients and their relatives to report at once any unusual fatigue, weakness, sore throat, or any evidence of illness or infection. Should any of these symptoms appear or should the patient suffer an intercurrent illness, especially after the first month of treatment, frequent leukocytes and differential counts should be made until the patient is well. Therefore, it is mandatory that ambulatory patients receiving Thorazine should be supervised closely.

Thorazine should be stopped when agranulocytosis is detected. The patient should receive antibiotics and ACTH. Transfusions are optional. Most cases recover within two weeks. If further psychiatric treatment with a tranquilizing drug is indicated, a Rauwolfia derivative should be substituted. Under no circumstances should the patient who has had Thorazine agranulocytosis be re-treated with this drug. This clinical law is based on previous experience with other drugs that induce agranulocytosis.

COMMENT

The majority of dermatologic and systemic reactions to Thorazine occurred in women. The significance of this observation is unknown at present. These expressions of drug sensitivity with the exception of agranulocytosis usually are not serious. They are temporary reactions seldom requiring discontinuation of Thorazine and are not a positive contraindication to re-treatment with Thorazine.

SUMMARY

This paper presents the various dermatologic and systemic manifestations of Thorazine hypersensitivity encountered by the author in 500 patients. It indicates that these side effects are allergic reactions related to the chemical structure of Thorazine. Emphasis is placed on the clinical significance and management of these reactions, particularly jaundice and agranulocytosis. The literature on this subject is reviewed

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SOCIETY PROCEEDINGS

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

Meeting of March 22, 1956

Dr. Wilfred Bloomberg, President, Presiding

Upper Thoracic Cordotomy for Relief of Pain: Postmortem Correlation of Spinal Incision with Analgesic Levels in 18 Cases. James C. White, M.D., Edward P. Richardson, Jr., M.D. and William H. Sweet, M.D. (published in full in *Annals of Surgery*, September, 1956.)

We have been able to examine postmortem the exact position and extent of the cordotomy incision in 18 patients who have survived for periods from a week to four years. These lesions are illustrated by photomicrographs and diagrams and are correlated with the clinical level and loss of sensibility to pain.

It is evident that the position of the axons which conduct pain is very variable. The ascending pathways for the perception of pain may occupy the greater portion of white matter in each anterior quadrant. It is unfortunate that the tract is rarely condensed into a compact bundle of fibers between the dentate ligament and the line of emerging ventral rootlets, as illustrated in current neuroanatomical and surgical texts.

While the greater portion of sacral pain fibers tend to lie most posteriorly and laterally, just in front of the dentate ligament and medial to the thin crescent occupied by the ventral spinocerebellar tract, the thoracic fibers most ventromedially, and the lumbar fibers in between, we have found that scattered fibers from the buttocks and legs lie well anterior and medial to the motor roots. In rare instances pain in the lumbosacral area has not been relieved by an apparently complete destruction of the contralateral anterior quadrant. A possible explanation for this is that pain-conducting axons may run uncrossed in the ipsilateral spinothalamic tract at least as high as the upper thoracic region.

Degeneration of fibers is often seen far posterior to the dentate ligament in the peripheral portion of the pyramidal tract; at times in the base of the posterior columns, and on three occasions across the median ventral sulcus. This appears to have resulted from contusion of the sensitive white matter by rotation of the cord or compression by the cordotomy hook. In one instance extensive injury to the lateral and dorsal columns appears to have been related to an unusual posterior attachment of the dentate ligaments.

The more extensive transections of white matter have resulted in higher and more consistent levels of analgesia, as well as in much more effective and enduring relief of pain.

Despite these radical incisions, the incidence of disagreeable complications has been infrequent. Only a single patient suffered from persistent leg weakness and one of nine bilateral cordotomies has led to prolonged difficulty with urination. One unfortunate individual complained of a sense of burning hyperpathia in the area of analgesia. This unusual, but most distressing complication of cordotomy may have been related to extensive destruction in the posterior portion of the cord.

We conclude that the effectiveness of cordotomy can be increased if the surgeon carries his transverse incision ventral to the dentate ligament to a depth of 5 mm. (nearly to the midline) and cuts across the anterior quadrant to a point at least 2 mm. medial to the emerging line of motor rootlets. This more radical transection involves no added risk of complications provided care is taken not to injure the anterior spinal artery or the postero-lateral and posterior columns of white matter.

Discussion—Dr. William H. Sweet: In order to get more information on pain conduction we have inserted tiny electrodes into the cord with the patient awake. The sensation provoked at low voltage on stimulation in the region of the anterior quadrant is, oddly enough, comparatively mild. It is usually described as some form of sensation of pain or temperature, as one could expect. But if one stimulates electrically the posterior surface of the posterior columns this produces an intensely disagreeable, usually tingling, sensation. Stimulation within the anterior half of the cord has occasionally evoked ipsilateral pain referred many segments below the level of the electrode so that there was no question about inadvertent stimulus to an entering posterior rootlet. In one patient in whom two cordotomies contralateral to one-sided pain had proven unsuccessful we obtained such ipsilateral responses upon stimulation within the cord and took this as a cue to make an incision ipsilaterally in the cord. This happily yielded relief of the pain. We were thinking of doing an ipsilateral cordotomy on patient H. D. G. mentioned here, the patient who at postmortem had a zone of preserved fibers only 0.5 mm. wide along the anterior median sulcus. In him it seems likely that his unilateral ano-genital pain was being transmitted by secondary afferent neurones placed ipsilaterally in the cord rather than by the contralateral fibers lying in the position of the uncrossed corticospinal motor path.

Dr. James C. White: We learned one thing from Dr. Putnam. When he was severing the pyramidal tract in Parkinsonism he would insert the knife just lateral to the point of emergence of a posterior rootlet and cut down nearly to the dentate ligament. Despite such an extensive transection of the motor tract the patient would be hemiplegic for only a week or two.

He would then soon regain sufficient strength to walk. It is remarkable that you can injure so much of the corticospinal column and not produce more serious weakness of the leg. In our total cordotomy statistics only 4% developed notable leg weakness after a unilateral operation. In last January's number of ***Brain*** Nathan and Smith illustrate diagrammatically the extent of transection in a series of postmortem examinations after antero-lateral cordotomy. They show a very similar degree of degeneration dorsal to the dentate ligament. They correlated this only with the presence or absence of a Babinski response, not with the degree of weakness in the leg.

Dr. Jerome K. Merlis: I should like to fish for a little information. In the course of some experiments in the cat, I had the opportunity to record from the nucleus ventralis postero-laterlis of the thalamus. I noted that both ipsilateral and contralateral pin-prick would evoke a response. I have only made a few such observations and do not know whether or not it is the rule. Do you know whether this is consistent in the cat, and are there such species differences in the thalamic representation of pain?

Dr. William H. Sweet: A number of investigators have concluded that the pain pathways in the cat's spinal cord are more diffuse than those of man. Of course one cannot be sure if the movements a cat makes are indicative of pain. However, Karplus and Kreidl (1925) could not eliminate responses to noxious stimuli applied to the hind legs of their cats even by complete hemisections on the two sides of the thoracic cord five or more segments apart. The legs appeared to be analgesic only when the hemisections dividing the cord were separated by four or fewer segments. From these observations they concluded that pain impulses in the cat travel in short chains with much crossing from side to side.

Dr. Jerome K. Merlis: In monkeys?

Dr. Sweet: Mott (1892) divided in monkeys the anterior half of the spinal cord on one or both sides. Postoperatively he could find no evidence of loss of pain sensation. Studies on dogs have been equally misleading as to the effects likely to be seen in man. Cadwalder and Sweet (1912) made careful pre- and postoperative canine examinations and found after thoracid anterolateral cordotomy evidence of incomplete loss of cutaneous pain sensibility plus profound ataxia of the hind legs. Histological analysis revealed operative lesions of the locus to the extent which in man usually produce cutaneous analgesia without ataxia.

Dr. D. Denny-Brown: I have two anatomical questions for Dr. Richardson. The root exit zone did not happen to appear in the sections shown. The ventral extent of the lesion seemed to be 2–3 mm. lateral to where I would expect the ventral root to emerge, namely about opposite the middle of the anterolateral edge of the ventral horn.

My second question is whether pallor in myelin stained sections accurately represents the extent of the lesion. In experimental lesions of spinal cord in the monkey I have had great difficulty in delineating the exact extent of the lesion, if survival has been short. Within the first two weeks, there is a zone where myelin stains poorly around the whole line of destruction. The same type of lesion after three months, will show a clear-cut edge in myelin stain. In the early stage charting the extent of necrosis with ordinary tissue stains would appear to me to give a more reliable estimate of extent of lesion. It would seem to me that abnormal conduction through partially damaged tracts at the edge of the lesion might give rise to dysethesias.

Dr. Richardson: It should first be pointed out that the anatomical studies are not yet entirely completed, and that the illustrations shown on this occasion, and the only ones now available, do not necessarily show the full extent of the cordotomy. With respect to the extension of the cordotomy lesion to the anterior root exit zone, it is true that in some cases it did not reach that far anteriorly—even though some of the anterior root fibers emerge more laterally than might be thought. In such cases, pain relief was incomplete, or the level of analgesia was low.

Dr. Denny-Brown is perfectly correct in stating that the zone of pallor in myelin-stained sections does not necessarily represent the true extent of the lesion. We have been able to study the lesions in our material in serial cross-sections, and have taken the limits of the lesion to be those of the region of total tissue destruction. It is generally not possible to demonstrate the full extent of the zone of totally destroyed fibers in any one section or photograph because the cordotomy incision is generally not absolutely perpendicular to the long axis of the cord, but rather somewhat oblique. Extending beyond the limits of the region where fibers were totally severed is one in which some damage has occurred, but it is incomplete; it is this region which shows pallor of myelin staining. Dr. Denny-Brown's suggestion that dysesthesiae might arise from abnormal conduction through such damaged pathways is an interesting one that must be given serious consideration.

Dr. Sweet: I should like to make another point about the emergence of the anterior rootlets which has been emphasized by Kahn. These rootlets do not come out along a linear anterior median sulcus. Instead a cross section of the cord shows some of them passing straight ventrally from the lower medial corner of the anterior horn of gray matter whereas others come out more and more lateral to this, some passing almost straight laterally from the lower lateral corner of the anterior horn. The site of emergence of an anterior rootlet from the cord is consequently an unsuitable landmark for a precise incision within the cord.

Dr. White: We had 20 patients with long survival periods, 1–5 years. Those people showed no change in vibratory sense, no change in graphesthesia, no change in two-point discrimination. A few of them would feel hairs equally on the analgesic and normal sides. Some might have to have a hair three times heavier. It seems odd that at least half the cord should be given over to conduction of pain and temperature sensation.

Dr. Paul I. Yakovlev: I wish to comment on the organization of central conduction paths in the spinal cord for various modalities of sensory experience. There is a natural tendency to envisage these conduction paths in terms of wiring diagrams. In reality, however, any centripetal sensory excitation once beyond the first synapse may propagate through the entire spinal cord as a universal path to the brain. It is only gradually in the course of phylogeny that the conduction of certain modalities of sensory experience becomes committed to certain anatomically specific long central paths at the exclusion of other paths. There is a gradient in the differentiation of sensory experience from the universal excitability of all living matter to highly specific (particular) excitability to stimuli such as visual, tactile, and proprioceptive. These latter modalities of sensory experience are committed to central conduction paths which are anatomically and physiologically highly definitive and correspond almost literally to wiring diagrams of a central telephone board; in the case of visual experience the central conduction path becomes so specific and space committed that it is emancipated from the brain (optic tract) and appears as if it were a peripheral nerve (optic 'nerve'). But in the case of pain experience, the most universal modality of experience conceivable, the principle of universality in the organization of central conduction through the spinal cord is largely maintained. The important anatomical fact is that the lateral spino-thalamic tract is a polyneuronic system of multiple, overlapping synaptic relays allowing for a wide diffusion of conduction through the spinal cord. In the gamut of experiences which we qualify as pain there are some modalities of pain experience which are more specific, i.e., less universal than other modalities of pain. Such is the so-called 'fast pain' of a pin-prick applied to the skin. This relatively specific pain experience is probably conducted through long myelinated fibers of the lateral spinothalamic tract. However, according to all available evidence even in man there are very few of such long neurons in the lateral spinothalamic tract. The so-called 'slow' more universal modality of pain experience, slowly building up from temporal summation of successive subliminal stimuli and outlasting them, is conducted slowly through the huge synaptic surface of multiple relays in the reticulate matrix of the grey matter of the spinal cord and brain stem. The conduction of these modalities of universal pain is not committed to specific long paths. These anatomical and physiological considerations apply to descending systems of conduction as well. The space committed specificity of conduction from the central cortex to the anterior horns through the cortico-spinal (pyramidal) tract in primates and man differentiates gradually from a diffuse universal conduction through any available open central paths. In a rat the cortico-spinal fibers are scattered through the entire cross-section of the cord in multiple bundles running through the dorsal as well as the lateral and ventral funiculi.

Dr. Sweet: In the "analgesic" zone following a cordotomy we have always been able to evoke a disagreeable sensation by stimulation of the skin with bipolar electrodes 2–3 mm. apart carrying a 60 cycle current at 40 to 140 volts. Less frequently other stimuli may produce pain in the otherwise analgesic zone; examples of stimuli capable at times of eliciting pain in an area analgesic to vigorous single pin prick are: 1) compression of an Achilles tendon, 2) testicular compression, 3) pressure against bone (50 lbs./sq. in.) 4) hair pulling and 5) multiple rapid pinpricks.

Notes on the Medical History of the Ventricular System and Cerebrospinal Fluid. Louis Bakay, M.D.

There is no abstract for this paper available.

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

Meeting of April 20, 1956 with Dr. Wilfred Bloomberg, President, Presiding

Neuropathological and Neurosurgical Aspects of Postnatal and Natal Cerebral Injuries. C. E. Benda, M.D. and G.-F. Hoessly, M.D.

1. Among the causes of mental disorders of childhood, so-called "cerebral palsies", blindness and mental deterioration, a considerable role is played by injuries to the brain at the time of birth and early in life.

2. The case of an 18-months-old infant who fell thirty feet from a second-story porch to a cement sidewalk and developed unconsciousness, paralysis, and finally blindness, is presented in detail, with neurosurgical procedures immediately after the accident and clinical and neurological observations over a period of 2 years and 9 months to the time of death, after which a careful neuropathological study was made. The case revealed evidence of the late effects of a concussion of the frontal lobes, and severe encephalomalacia and cystic degeneration of the whole occipital and parts of the parietal lobes in connection with a greatly thickened dura and formation of fluid sacs within the dural sheaths. The mechanism and significance of this pathology are discussed.

3. Two cases of paranatal injuries and one of a brain trauma a few days after birth, with similar pathology, are presented and a summary given of six cases of cystic degeneration of the brain.

4. Birth injuries and traumata early in childhood are serious because the lesions interfere with a rapidly growing brain, the development of which is constricted and the immature brain tissue deprived of proper circulation and nutrition, undergoing rather rapid degenerative changes. Among the neuropathological lesions, cystic degeneration of the white matter and encephalomalacia of the gray matter are both most conspicuous. The progressive character of the lesions explains the progressive deterioration and gradual development of blindness observed in several of these cases.

5. The early diagnosis of brain injuries in infancy and childhood is discussed, and a more active neurosurgical approach suggested.

Discussion—Dr. Paul I. Yakovlev: Most of us, I am sure, appreciate the always practical slant in Dr. Benda's investigations in the field of pathology of children in which he is so rightfully eminent. I hope that neurosurgeons would make more authoritative comments than I can do on the issue of indication of extensive surgical intervention in the case of severe head injuries in children. It seems to me that in the case of infants and young children, the neurosurgeons would be understandably doubly cautious because whatever happens in the future may be attributed to the operation per se as well as to the accident of injury. It would seem clear, however, from what Dr. Benda said that in view of so much being at stake for the child, the personal risks should be taken beyond what in the circumstances might be considered a reasonable risk. I would like to ask Dr. Benda whether he feels that on the whole infants tolerate and adapt functionally to cerebral injuries and surgical intervention much better than adults. I have seen some remarkable examples of a complete or nearly complete functional recovery even following what seemed at the time to be a hopelessly crippling damage to the brain.

Dr. Joseph M. Foley: Dr. Benda, what is the evidence that oxygen can produce hyperemia, congestion and subdural or epidural bleeding? It seems very improbable to me.

Dr. D. Denny-Brown: I want to question that, too. Oxygen does not cause congestion of the brain in the experimental animal. I question whether oxygen after birth at maturity has any adverse effect. I would like Dr. Benda to qualify his statement that 24 per cent of mental and spastic defect is related to birth trauma. In such patients in our outpatient clinics, I would think the figure is much lower. The severe symmetrical damage to the occipital and related cortex in Dr. Benda's case raises the question of damage to the posterior cerebral arteries resulting from herniation by the subdural lesion at the beginning of the illness. It appeared to me to be consistent with ischemic necrosis.

Dr. Bertram Selverstone: Drs. Benda and Hoessly may be interested to know that we have observed on a number of occasions that the administration of 100 per cent oxygen along with hyperventilation will "shrink" the brain quite considerably at operation. This technique can be very useful when it is necessary to expose a deep structure along the base of the skull. There appears to be considerable vasoconstriction under these circumstances, probably due more to hypocapnia than to hyperoxygenation. The question also arises as to whether there is any reluctance to perform major neurosurgical procedures at a very early age. Newborn infants tolerate major procedures, both intracranial and spinal, extremely well. The problems which arise in these infants who have had severe intracranial hemorrhages during the process of birth have to do with the fact that bleeding is often multifocal in origin, coming from tears in the bridging veins, the dural sinuses and small arteries as well. It would be necessary to perform several craniotomies in order to expose all the sites, in many cases. Most of us feel, therefore, that multiple tapping during the phase of acute bleeding will tend to keep the pressure down while the lesser veins and perhaps some of the small arterial sources subside of themselves. Then, if necessary, any major source can be dealt with hours or even days later. Perhaps another problem in this community is the separation of obstetrics and neurosurgery since obstetrics is so often done in specialized hospitals and the patients are not seen by the neurosurgeon as early as Dr. Benda would like. To my mind, the most important problem is however, one which we really can't deal with. In my experience, contusion and laceration of the brain are features which are more prominent and of more importance than the hemorrhage and clot formation. I do not think that operative measures can offer much help for this aspect of the problem. These birth injuries have much in common with the so-called acute subdural hematomas seen so often in adults after motor accidents. Actually, these patients are suffering from cerebral contusion and laceration as the major injury and the subdural hematoma is incidental. The mortality of this lesion is very high as compared with the extremely benign course of the patient who is operated upon for chronic subdural hematoma.

Dr. Benda: I am very thankful to the different discussants because the main purpose of this presentation was to stimulate interest of the different branches of medicine dealing with the neuropsychiatric aspects of childhood and especially with the sequela of traumata.

As to Dr. Yakovlev's question, I may say that I have had the same experience that some children recover extremely well after a birth injury or injuries later in life, and I am still looking for indications of how we can make an early differentiation of the prognosis. It is also our experience that the immature brain reacts to an injury in a different manner than an adult. I am inclined to believe that the glia of the infantile brain is less resistant to external injury and, therefore, seems to be adversely affected, often in the same manner as the brain cells so that the glia loses its ability to respond to injury and provide reparatory processes. I think that Dr. Spatz proposed such a theory years ago, and I think that many observations bear out the correctness of his ideas.

As to Dr. Denny-Brown's question about the percentage in our material, I have to refer to several of my publications in which I have tried to analyze our autopsy material. Of course, our autopsy material is "biased" for the reason that it represents a selection of cases that have been institutionalized for reasons of mental deficiency. Moreover, I have always emphasized that the number of 25 per cent of evidence of vascular circulatory anomalies and injuries refers to the cases of severe mental deficiency and not to the whole population seen in a neuropsychiatric outpatient clinic. In such a clinic, one sees a great number of different conditions in which the brain-injured children only form a smaller percentage.

I am sorry that my remarks about the circulatory anomalies under the influence of oxygen were not clear enough, due to the shortness of available time. I am well aware that oxygen has a vaso-constrictor effect on the arteries and possibly the small veins, therefore causing vaso-constriction and diminished blood flow in those areas. It is, however, also true that if a certain area is hypemic due to vaso-constriction, the blood has to be somewhere else; and that if we have abnormal conditions with vaso-paresis as we see so frequently after birth injuries, the blood may be pressed into those areas and oxygen may have a very different effect from what it has under normal conditions. Moreover, there is a great difference between the temporary, short-time use of oxygen and the exposure to oxygen over a period of weeks and months. Although I am not able to provide evidence of the circulatory anomalies caused by the long-term administration of oxygen, it was my intention to suggest that as we see in retrolental fibroplasia, we may also find similar processes going on in the premature brain after long exposure to oxygen.

As to the demyelination which is so conspicuous in the material presented, I did not wish to call this a "demyelinating disease". I wanted to call attention to the occurrence of large areas of demyelination which depended apparently on the injury and which could not have been recognized in etiology except through the study of large hemisphere sections which provide evidence of the relationship between the demyelinated areas and the periphery.

We have not presented a theory for the details of pathology because before forming a theory, it seems important to observe many cases of this type and only a few have been available so far for study.

STUDIES ON THE MECHANISM OF COPPER DEPOSITION IN WILSON'S DISEASE. L. L. UZMAN, M.D.

Investigations in the past have shown that Wilson's disease patients are on a continuous positive copper balance (av. 0.5 mg/day). That this is due to over-absorption of copper by the intestinal tract also appears conclusively demonstrated. Equilibrium dialysis experiments to determine the avidity for copper binding by tissues were carried out by the author (in collaboration with Drs. F. Iber and T. C. Chalmers). Surgically removed liver tissue from a case of early Wilson's disease was compared with similarly obtained liver tissue from two normal subjects. It could thus be shown that the avidity of the liver for ionic copper was much higher in Wilson's disease. It was also shown by electrophoretic studies that this avidity for abnormal amounts of copper binding could be traced to an electrophoretically distinct fraction among the soluble liver proteins in Wilson's disease. In three other cases of Wilson's disease the author was able to show histochemically a marked difference in the copper content of adjacent lobules. There was a distinct difference in the electrophoretic patterns of lobules with high copper content as compared with those of low copper content. However, those lobules with low copper content still possessed the protein fraction characterized by a high avidity for copper. It is concluded that the avidity for copper resides in a structural abnormality of proteins in Wilson's disease, and that the deposition of copper is secondary to a fundamental defect in protein metabolism.

Discussion—DR. CHALMERS: When Dr. Uzman asked me to come tonight and discuss his paper, I was reluctant to oblige him because I am neither a neurologist nor a biochemist. However, I have been observing from the outside the progress that has been made in the last few years in delineating the pathogenesis of Wilson's disease, and I have been interested in the aspects associated with the liver. As you probably know, there are at least two schools of thought about the relation of copper to the pathogenesis of Wilson's disease. On the one hand, Dr. Uzman has shown you very beautifully tonight some excellent evidence that there is in Wilson's disease a primary defect of protein with a markedly increased affinity for copper. On the other hand, Bearn and Kunkel, and Cartwright and Mahoney believe that the primary defect is one of an inability to manufacture ceruloplasmin, and this deficiency leads to an increased absorption of copper and excessive deposition in the liver and kidneys, with a resulting cirrhosis and kidney tubular damage, the latter manifested by aminoaciduria. I was planning to review briefly the data presented by Cartwright, Mahoney, and others as part of my discussion of Dr. Uzman's paper, but I see Dr. Mahoney in the audience, and I am sure he is better able to present his point of view than I.

I should like to ask Dr. Uzman and Dr. Mahoney how they might explain the paradox that *in vitro* the liver of patients with Wilson's disease has an increased affinity for copper, and *in vivo* the isotope copper 64 disappears from the circulation less rapidly than in normals.

I wish to make one point about the techniques we have seen tonight. At least 5 per cent of patients with Wilson's disease die without ever developing any neurological abnormalities, and a patient recently studied by us had none, not even any changes in her brain at autopsy. It seems possible that many patients previously diagnosed as juvenile, or familial juvenile, cirrhosis have had a form of Wilson's disease, and the copper stain demonstrated tonight offers a convenient and simple way of distinguishing these patients from those with simple cirrhosis of the liver.

Dr. Uzman should be congratulated for continuing his significant contributions to the pathogenesis of this fascinating and disheartening disease.

DR. JOHN P. MAHONEY: This represents a refreshing new approach to the study of a most interesting disease process. Most of us who have been studying this disease have been impressed by our inability to establish a single concept which would explain all of the biochemical abnormalities. This work at least represents a new piece of factual information. At the moment I am unable to explain the apparent discrepancy which exists between Dr. Uzman's *in vitro* observation and our own observations *in vivo* that radiocopper is cleared from the plasma less quickly in patients than in normal subjects. In addition normal subjects seemed to localize radioactivity over the liver site after injection of tracer qualities of radiocopper, while the patients showed no such localization. The latter observation led us to postulate that the patients' livers were so saturated with copper that they could absorb no more.

I wonder if Dr. Uzman has studied any other tissues by the techniques demonstrated. The possibility exists that the increased absorption of copper in Wilson's disease is due to some abnormality of the mechanism whereby copper is transported across the intestinal membrane. Demonstration of an abnormal copper containing protein in the intestinal mucosa might be a clue to the nature of this absorptive defect. In the past it has been suggested that the increased copper absorption was due to the low levels of ceruloplasmin. Our studies demonstrated no correlation between the level of ceruloplasmin and the rate of absorption of copper.

I should like to compliment Dr. Uzman on his work.

DR. D. DENNY-BROWN: Dr. Uzman's studies have focussed attention on the question of protein binding of copper, and in the liver the staining of the liver cells was therefore of great interest. But the same stain applied to the nervous system shows the glia to be stained, not the nerve cells. The Kayser-Fleischer ring is also related to staining of interstitial tissue. Our original idea that Wilson's disease of the nervous system is primarily an alteration of glia appears to be correct. The question therefore arises whether the changes in the liver are related to the excretory function of that organ. The liver is the normal channel for excretion of copper. We found that the bile of patients with Wilson's disease has a normal copper content. The perinuclear structure that begins to stain for copper has the appearance of the Golgi apparatus. As it becomes overstained, then the cell becomes degenerate, suggesting a block in the excretory system in the cell and ultimate degeneration of it. This process is not necessarily representative of cellular changes in other organs.

Dr. Alfred Pope: I would like to ask about the nature of the copper complexes presumably formed in the tissues. Does copper form chelate rings with amino acids and peptides, and if so, what would be the nature of the coordination complexes with the amino acid residues in the peptide chains of the protein? Also I wonder whether you would care to speculate concerning the alteration of liver protein structure that might underlie abnormal copper binding capacity.

Dr. Uzman: I will endeavor to answer Drs. Chalmers' and Mahoney's questions together. In talking about the binding of substances by proteins one has to remember that we are dealing with an equilibrium phenomenon which is determined by a number of factors. In general, the amount of substance X bound by protein Y will be determined by the amount of X still free to bind unless the protein is already fully saturated. Thus caeruloplasmine, which is fully saturated in its copper binding capacity will not bind additional copper, but will liberate additional copper if dialyzed under appropriate conditions so that a copper-free "apo-caeruloplasmin" is obtained. This is not an oxidative enzyme anymore, nor is activity restored by adding copper. Presumably its immunological properties are also lost. Thus, the amount of copper bound by a cell is mainly a function of available binding sites, concentration of free copper ions outside the cell, and the strength with which copper is bound at the available sites. The last factor is especially important in radioactive copper work, where presumably a great portion of the recorded uptake of Cu-64 by an organ, may only represent "exchangeable" copper and not additionally bound copper. This may explain the slow apparent loss of radioactive copper from the plasma of patients with Wilson's disease. Hence it is difficult to reconcile the discrepancies between the actual high affinity for copper of tissues measured directly, as reported here, and results of *in vivo* work where none of the factors determining the amount of Cu-64 bound are known. For example, in a given patient whom Cu-64 is administered, we have no idea what his liver copper picture is like. In histochemical procedures as shown today, would all his lobules appear black, some black and some white, or all white? One thing we do know, all the copper appearing in the urine in this disease has to come from tissue and is not derived from freshly ingested copper as Matthews' and others' work has shown.

With respect to Dr. Mahoney's second question, I have recently had occasion to study two renal biopsy specimens from Wilson patients kindly sent by Dr. Kark of Illinois. In neither was the copper above normal.

Dr. Denny-Brown's suggestion is a very interesting one, and one to which I have myself subscribed. I believe that the increased copper binding capacity described for liver, is a property of all tissues in this disease, thus also, if a given dose of Cu-64 is injected there is no guarantee that it will not be taken up by other tissues first. Another point that renders the value of such data doubtful.

What worries me most about the glial changes in the CNS, that Dr. Denny-Brown mentioned, is their general significance in terms of the whole disease process. We do know that the disease can manifest itself in families with only liver involvement and without neurological involvement for many years. Perhaps the stigmatized protein abnormality in different cells and cell systems, varies in degree and amount present.

Dr. Pope's question regarding the type of groupings on the liver proteins which are responsible for the increased affinity for copper is a hard one to answer. From the analogy of oligopeptide-copper chelates found in the urine, I am tempted to say that these peptides with copper chelated to them represent fragments of tissue protein breakdown, and that since these peptides have dicarboxylic amino acids as N-terminal residues, the chelation is probably due to a carboxyl-metal ligand. *In vitro* studies in which competing anions (organic phosphate, sulfate, carboxyl) are offered to remove copper already bound may give a clue as to the type of chelation involved.

I would like to thank all the discussors for the interesting points raised.

OBITUARY

Ester Loring Richards, M.D.

1885–1956

Dr. Ester L. Richards died at her home in Baltimore on July 6, 1956 at the age of 71 years. She was a psychiatrist of wide reputation in the field of mental hygiene and from 1920 to her retirement in 1951 was in charge of the Outpatient department of the Phipps Psychiatric Clinic of the Johns Hopkins Hospital. During this period she was also Associate Professor of Psychiatry in the Hopkins Medical School where she had graduated in 1915.

Dr. Richards was popular as a lecturer in her field where she had particular interests in community service and in the emotional disorders of children. Having been trained in psychiatry by Adolf Meyer, and closely associated with him and his work over many years, she followed closely the Meyerian theories and methods in her professional activities.

During her active career she published numerous articles in scientific periodicals and was the author of two books, one entitled "Behavior Aspects of Child Conduct" published in 1932 and another "Introduction to Psychobiology" which appeared first in 1946. In 1946 she was chosen by the Women's National Press Club as one of the ten outstanding women in America. Psychiatry has thus lost an able clinician, a stimulating teacher and a tireless worker, and America has lost one of her famous women.

BOOK NOTES AND REVIEWS

Books received are acknowledged and given a brief description in this section. Selections serving a variety of interests will be made from these for a more extensive review, as far as space will allow.

BOOK NOTES

Conel, J. LeRoy. The Postnatal Development of the Human Cerebral Cortex. Volume V. The Cortex of the Fifteen-Month Infant. [Cambridge, Mass.: Harvard University Press, 1955 Pp. 235 + cix plates (235 figures). $12.50.]

This beautifully designed book represents an enormous amount of detailed scientific investigation which has been well organized and clearly written. It is the fifth volume in a series by Dr. Conel, the first volume of which presented the histology of the cerebral cortex of the new born infant. This was published in 1939 and since then the author has been following progressively the different stages of growth and development of the cortex. The results of these studies show a painstaking, systematic recording and description of the histological findings.

The illustrations consisting of liberal photomicrographs of cortical structure and drawings of cell organization from Golgi-Cox preparations are excellent as are also the actual size photographs of the gross aspects of the 15 months old brain.

Although the present state of knowledge of the correlations between cortical physiology and the structures so well illustrated here in detail, does not carry us very far, it is extremely important to have the anatomical background ready for a future use which is bound to come sooner or later. Dr. Conel is doing neuroanatomy and neurophysiology a great service by his masterly researches. All those concerned with the study of cerebral structures and function should have these volumes on hand.

Hoerr, Normand L. and Osol, Arthur (Editors). Blakiston's New Gould Dictionary (Second Edition). [New York: McGraw-Hill, 1956. Pp. 1463, Illustrated. $11.50.]

The first edition of this outstanding medical dictionary appeared in 1949. This second edition has been fully revised and has expanded 179 pages comprising thousands of new terms and other useful additional features. The practical tables in the appendix have been enlarged and a table of isotopes included. In one section there is an index of 45 full page plates, over half of which are in color. In creating this edition an editorial board and 88 contributors with their combined efforts have produced a medical dictionary that will serve adequately all branches of the profession as well as numerous other scientific disciplines. These efforts should be much appreciated and, by the way, here is a lot of book for the price.

Homburger, F. The Medical Care of the Aged and Chronically Ill. [Boston: Little, Brown and Co., 1955. Pp. 253. $5.75.]

This book presents in a clear, easily readable style an account of the problems arising in the management of that most important group of disorders, the chronic illnesses and their complications in the different organ systems.

Among the special sections are those devoted to osteoporosis, to various forms of arthritis, to problems of nutrition, to the management of cancer, to the forms of paralysis, and to nursing problems inherent in chronic illnesses.

The text is direct to practitioners, students and nurses all of whom will derive a great deal of help from the wealth of practical suggestions for the care and comfort of unfortunate invalids and aged persons. We are glad to recommend it to all who have to meet these problems professionally.

Brain, Sir Russell and Strauss, E. B. Recent Advances in Neurology and Psychiatry. (Sixth Edition). [Boston: Little, Brown and Co., 1955. Pp. 311, figs. 46. $7.50.]

This sixth edition of a very useful book is a thoroughly new work that reviews the recent contributions in the field of neuropsychiatry. Through fourteen chapters the text presents research and clinical information on the lobes of the brain, on consciousness and unconscious phenomena on several diseases including infections and demyelinating disorders, and on cerebral circulation.

There is a short but informative chapter on the cerebellum, an excellent chapter on electroencephalography by Dr. Dennis Hill, one by Dr. David Sutton on neuroradiology and one by Dr. Douglass Northfield on intracranial tumors which discusses neurosurgical and radiotherapeutic issues.

The volume is well documented and adequately indexed. It will be of great aid to those busy practitioners who have too little time or opportunity to keep up with the literature. Neurologists will find it a comprehensive review of their specialty.

BOOK REVIEWS

Sartre, Jean-Paul. BEING AND NOTHINGNESS: AN ESSAY ON PHENOMENOLOGICAL ONTOLOGY. Translated and with an introduction by Hazel E. Barnes. [New York: 1956. Philosophical Library, pp. lxix + 638. $10.00.]

The chief aim of an ontologist is to answer the question: what exists and how does it exist. Sartre, the founder of existentialism, has given an answer which, in many aspects, is new, original, and challenging. He has been influenced in his thinking by the most striking developments in modern psychology and physics as well as by Descartes, the first philosopher to make the problem of knowledge the foundation of ontology, and by the other great thinker of the past whose best efforts were devoted to the study of the relation between knowledge and reality, Immanuel Kant. Sartre seeks to get away from what Nietzsche called "the illusion of worlds behind the scenes" in all aspects of life and to be a pure phenomenologist. Realizing comparison is the indispensable condition of all judgment, including psychological phenomena and ethical evaluations, Sartre looks upon opposites not as excluding each other but as requiring each other. Thus "good" would make no sense and would have no existence without "evil", "fact" without "thought", "truth" without "falsehood", and even the awareness of being without the awareness of nothingness. The difference between the terms of each pair of opposites, ontologically, therefore cannot be one of kind but of degree; it is a difference in intensity or in the degree to which "real possibilities" are unfolded or manifested at any one moment in time.

Like Hegel, Heidegger and Husserl, Sartre assigns new and unfamiliar meanings to old terms. Thus "essence" is defined as every individual's past. Since there is no predetermined development of human beings, each person creates his essence as he lives; in other words, since no one lives in exactly the same conditions, he is shaped differently in his travel through time and space. The terminology is not the only reason why the utmost concentration is required if one wants to understand and follow Sartre. His is a book that is hard to read. He defines "nothingness" as a recoil from fullness of being. To nihilate ("neantir") means to cause a state of non-full being and thus create consciousness. This line of reasoning leads, among other things, to the conclusion that "suicide is an absurdity", i.e, meaninglessness. "Life decides its own meaning because it is always in suspense; it possesses essentially a power of self-criticism and self-metamorphosis which causes it to define itself as a 'not-yet' or, if you like, makes it be as the changing of what it is. The dead life does not thereby cease to change . . . its meaning does not cease to be modified from the outside" by others. The unfulfilled possibilities are "nothingness" but they are also "freedom". Man is not his full possible being and this incompleteness is his "freedom" as well as a necessary condition of his capacity to be conscious of his possibilities. Thus "nothingness" makes man "free" and it also presses for completion or for an intensification of being, this pressure increasing with deepening consciousness. The state of nothingness is one of freedom as well as of frustration or pain.

Descartes' famous "I think, therefore I am" means, as Sartre points out, "I am aware that I doubt, therefore I am". The Cartesian "cogito" is reflective because it pertains to an object of thought and to doubt or negation regarding the existence of this object, but it is not a consciousness of the doubting thinker himself. Sartre wants to go beyond this reflective consciousness of external objects and reach the primary consciousness, the consciousness of oneself, the pre-reflective "cogito". Not only thought processes but also bodily phenomena are "pure facts of consciousness". Sartre avoids solipsism by positing that "this relation which I call 'being-seen by another' . . . represents an irreducible fact which cannot be deduced either from the essence of the Other-as-object, or from my being-as-subject . . . 'Being-seen-by-the-Other' is the truth of 'seeing-the-Other' ". Contact with others and their look, the others' watching us, are indispensable to make us aware of our possibilities on an unreflective primary level. Since most people are so dependent on the approval of others and since pain and anxiety are felt so much more keenly than other emotions, the usual subjective reactions to "the Other's look", observes Sartre, are "fear (the feeling of being in danger before the other's freedom), pride, or shame (the feeling of being finally what I am but elsewhere, over there for the Other), the recognition of my slavery . . . In so far as I am the object of values which come to qualify me without my being able to act on this qualification or even to know it, I am enslaved". Complete harmonious reciprocity of relationship is impossible and gives life a tragic aspect.

These seem to be Sartre's starting points for a philosophical system which is unique because its basic propositions are taken from modern psychology and psycho-pathology. There are many startling statements. Some of them have resulted from using old terms in a new sense and they cease to astonish when the reader grasps their content. However many formulations are novel and thought provoking. It is very likely that most readers will need to have read this large volume at least twice before they will be able to follow the author with comprehension. Dr. Barnes has translated the difficult text extremely well, has written a forty-page introduction which prepares the reader very well for the text, and has provided the book with a "key to special terminology" to which the reader will refer frequently to make certain he has not forgotten the definitions of the basic concepts. Sartre can be clever at times but he is also profound in many of his psycho-ontological observations and theoretical formulations. This complete philosophical Sartre includes also his "existential psychoanalysis". The courageous and tenacious reader will benefit from a study of this new ontology. This work must be evaluated separately from the person of the author. Sartre's political vagaries show that he finds it difficult not to be "enslaved" by others. What the ultimate effect and positive contribution of his ontology (as distinct from his practical and political activities) will be, only time will tell.

ZYGMUNT A. PIOTROWSKI

Grewel, F. PSYCHOPATHOLOGICAL ANALYSIS OF A CASE OF PICK'S DISEASE. [Amsterdam, Netherlands: F. Van Rossen, 1955. pp. iv + 106.]

Rare are cases of validly diagnosed Pick's disease, i.e., of a progressive cerebral atrophy which begins in the frontal lobes and gradually spreads to other brain areas. Still rarer are published individual case studies, especially when well worked up. Careful and detailed investigations of such cases constitute a most valuable and indispensable contribution to the study of irreversible intellectual deterioration. This investigation, supported by the Netherlands Organization for Pure Research, is one of several concerned with the Pick's disease. Holland seems to have given us the only genetic study of the disease (by Sanders, Schenk and Van Veen), covering four generations, in a family of which many members suffered from it. Dr. Grewel's patient had "an uneventful childhood". He sustained a brain concussion in a car accident at the age of 54. Two years later he begn to complain of forgetfulness, frontal headaches, uneasiness, and inability to stand any noise. He was examined for the first time at the age of 57. His condition grew rapidly worse. He died in 1941 at the age of 64. War conditions prevented an earlier publication of the case. The author knew the Goldstein and Katz case (Arch. Neurol. Psychiat., 1936) and examined his patient with the same and similar psychological techniques as those used by Kurt Goldstein, but he used also a number of other testing methods. The repeated neurological examinations are discussed in great detail as are the psychological ones. There is an excellent though brief chapter on differential diagnosis, which (because of war conditions) is not supported by autopsy. In the diagnostic discussion, Grewel summarizes and synthesizes the views of many authorities in the field.

The author's case differs in many psychopathological respects from the Goldstein-Katz case. Grewel is keenly aware of it and cautions against over-generalizations: "We must be careful not to speak too soon of one clinical picture of Pick's disease". On the other hand, the description of the Grewel patient's behavior shows numerous close agreements with the behavior of the Goldstein case (personally known and examined by this reviewer a number of times). The psychopathological peculiarities common to both patients are too subtle to be measured only by achievement on a standardized objective test because the patient's intention and verbalization as well as the objective test product must be analyzed to understand the nature of the patient's mental defect. Dr. Grewel made a real contribution which everyone interested in the process of irreversible mental deterioration will want to study closely.

Zygmunt A. Piotrowski

Grings, William W., Laboratory Instrumentation in Psychology [Palo Alto, California: The National Press, 1954, pp. vi + 282. $4.75].

As Dr. Grings states at the outset of "Laboratory Instrumentation in Psychology", a book which is described as being "an introduction to the laboratory directed at graduate students or professional people who desire enough detail to get started into an area of research", he intends the book to be an extensive, though definitely not all inclusive, discussion of many of the areas in which laboratory instruments are necessary or practical. In each instance, he discusses the types of instruments which are applicable, some of their characteristics, and at times weighs their advantages and drawbacks.

The reader may use the book for either orientation or reference. By reading it in its entirety, he will gain a marked degree of familiarity with the general field of laboratory instrumentation, its problems, its successes, and its lacks. If on the other hand, he desires information about some specific area, for example vision, the book serves well as a starting point for further study, and although the bibliography provided is by no means exhaustive, it will none the less prove a very adequate source of references to additional, more detailed discussions.

As the author indicates, some areas of instrumentation have been omitted. Specific mention is made of such areas as calculating and computing devices, laboratory use of animals, and the design and construction of one's own laboratory equipment. Dr. Grings feels, with justification, that these areas are either much too extensive to be dealt with satisfactorily in a general purpose book or that they have been presented sufficiently thoroughly in other sources.

It is apparent that, although written by a psychologist about equipment designed primarily for psychological laboratory use, there will be much of interest and profit to any who are undertaking research in the behavioral sciences. Of particular value are the chapters on behavior recording systems and on bioelectricity. These, researchers who desire to use various types of electronic apparatus and who desire a coherent discussion of their fundamental operating principles will find it of especial interest.

Barton W. Knapp

BOOKS RECEIVED FOR REVIEW

June, 1956

American Psychiatric Association. *Psychiatric Research Report 4.* Conference held at Galesburg State Research Hospital and the University of Illinois College of Medicine, Galesburg, Ill., September 16-17, 1955. American Psychiatric Association, Washington, D. C.

Cauldwell, David O. (Ed.) *Transvestism—Men in Female Dress.* Sexology Magazine, New York, N. Y.

Cooper, Irving S. *The Neurosurgical Alleviation of Parkinsonism.* Charles C Thomas, Springfield, Ill.

Gardner, George E. (Ed.) *Case Studies in Childhood*

Emotional Disabilities, Volume II. American Orthopsychiatric Association, New York, N. Y.

Grings, William W. *Laboratory Instrumentation in Psychology*. The National Press, Palo Alto, California.

Klein, D. B. *Mental Hygiene: A Survey of Personality Disorders and Mental Health*. Henry Holt & Co., Inc., New York, N. Y.

Lippman, Hyman S. *Treatment of the Child in Emotional Conflict*. McGraw-Hill Book Co., Inc., New York, N. Y.

Michal-Smith, Harold. *The Mentally Retarded Patient*. J. B. Lippincott Co., Philadelphia, Pa.

Milbank Memorial Fund. *The Elements of a Community Mental Health Program*. Milbank Memorial Fund, New York, N. Y.

Zeldenrust, E. L. K. *Über Das Wesen Der Hysterie*. S. Karger, A. G., Basel, Switzerland.

NOTES AND NEWS

VA. ENLARGED RESEARCH PROGRAM

A broader attack upon the "unknown" in man's major diseases will be started immediately by Veterans Administration.

VA said an enlarged medical research program will be conducted with the $10,000,000 that Congress appropriated for fiscal year 1957, beginning July 1, 1956—$4,300,000 more than was appropriated last year. Most of the increased medical research will be concentrated in four areas of major diseases: 1. mental, nervous and brain diseases (neuropsychiatric); 2. heart and artery diseases (cardiovascular); 3. cancer and leukemia, and 4. problems of aging (geriatrics).

VA also will expand its research program in tuberculosis, in the fungus diseases which resemble tuberculosis, and in the infectious diseases. In addition, renewed emphasis will be placed on individual research projects, such as the isolation and identification of the factors which produce man's greatest killer, hypertension or high blood pressure; the cause and nature of hardening arteries (arteriosclerosis); the cause and nature of tissue changes (metabolic diseases), and the brain areas where epilepsy and related nervous disorders originate.

VA further plans to enlarge its cooperative study of drugs, old and new, for the treatment of specific diseases—a field in which the agency has pioneered with outstanding success because of its many hospitals, its large patient load, and its uniformity of approach.

PROGRAM OF RESEARCH IN THERAPY

Twelve neuropsychiatric hospitals of Veterans Administration are prepared to conduct medicine's first extensive evaluation of mental patient care to learn which treatments best promote the improvement or recovery of mentally disturbed patients.

Dr. Jesse F. Casey, director of VA's psychiatry and neurology service, said each of the 12 hospitals has appointed a coordinator for its phase of the project.

Objectives: 1. To determine the relative effectiveness of different treatment techniques, such as drugs, electroshock, group psychotherapy, individual psychotherapy, and the various activity therapies now in use in VA hospitals. 2. To determine the relative effectiveness of different hospital designs, staffing patterns, and program emphases in the treatment of psychiatric patients; and, 3. To permit valid estimates of the relative costs of the various elements in effective treatment programs.

Dr. Casey said the project will be a cooperative one in which all of the 12 participating hospitals already have agreed on a uniform approach to the various evaluation goals.

The project director is Dr. Richard L. Jenkins, a psychiatrist with headquarters in VA's Mt. Alto hospital in Washington, D. C. Dr. Jenkins formerly was chief of psychiatric research in the VA Central Office at Washington.

THE HOFHEIMER AWARD

The Hofheimer Prize of $1,500 is awarded annually by the American Psychiatric Association for an outstanding research contribution in the field of psychiatry or mental hygiene which has been published within three years of the date of the award. The competition is open to citizens of the United States and Canada not over forty years of age at the time the article was submitted for publication; or to a group whose median ages do not exceed forty years of age. The next award will be made at the Annual Meeting of the Association in May, 1957. Articles submitted to the Prize Board before March 1st, 1957 will be considered. Eight copies of each publication and data concerning age and citizenship should be sent to Theodore Lidz, M.D., Chairman, Hofheimer Prize Board, 333 Cedar Street, New Haven, Connecticut.

LECTURE ON EARLY DEVELOPMENT

The third lecture in the Seventh Annual North Shore Health Resort Lecture Series on "The Medical Practitioner's Contributions toward Healthy Emotional Development

(The Physician as a Counselor)" will be held at the hospital, 225 Sheridan Road in Winnetka, Illinois on Wednesday, December 5, 1956 at 8:00 p.m. "Problems of Early Development" will be discussed by Lauretta Bender, M.D., Professor of Clinical Psychiatry, New York University, College of Medicine; Principle Research Scientist in Child Psychiatry, Department of Medical Hygiene, State of New York.

NFIP ANNOUNCES FELLOWSHIPS IN PSYCHIATRY

The National Foundation for Infantile Paralysis announces, among others, fellowships for the training of psychiatrists interested in the emotional problems of the physically disabled. Research and teaching interests in this area are highly desirable.

Only physicians, licensed, or eligible for licensure, to practice in the United States and who have had two years of graduate training in psychiatry acceptable to the American Board of Psychiatry and Neurology, are eligible.

Study is to be undertaken in a setting where medical and medical associate personnel are engaged cooperatively in a program of comprehensive rehabilitation. The facility should be affiliated with an established Department of Psychiatry approved for residency training by the American Medical Association and acceptable to the American Board of Psychiatry and Neurology. The Department of Psychiatry is to be responsible for supervision of the Fellow.

Financial support for the Fellow ranges from $3,600 to $6,000 a year depending upon marital status and number of dependents. Under unusual circumstances, higher stipends may be permitted. For a full academic program, complete tuition and fees are paid; for other programs, a sum not to exceed $1,250 including tuition may be arranged. All applicants must be citizens of the United States.

Applications must be received by March 1 for consideration in May, by September 1 for consideration in November, or by December 1 for consideration in February.

All awards are made upon recommendation of the appropriate National Foundation Fellowship Committee.

Fellowships in Psychiatry are a part of the National Foundation's Professional Education program which includes fellowships for social scientists interested in the emotional problems of the physically disabled as well as postdoctoral fellowships in the fields of research; orthopedics; rehabilitation; the management of poliomyelitis and preventive medicine.

In the associate medical fields, fellowships are awarded for physical therapists to prepare for teaching; and for health educators from State Health and Education Departments to study in an improved school of Public Health. In addition, scholarships are awarded for the basic education of medical social workers and physical therapists.

A limited number of two to three month fellowships are available for medical students who wish to take advantage of vacation time for study in research, public health and preventive medicine, or rehabilitation. This program is administered by the National Foundation through the Deans of the approved medical schools to whom inquiries should be addressed.

The National Foundation has authorized the expenditure of $23,500,000 since 1938 for scholarships and fellowships, and for aid to educational institutions, professional organizations, and related activities.

For further information write to: Division of Professional Education, The National Foundation for Infantile Paralysis, 120 Broadway, New York 5, New York.

ANNOUNCEMENT OF NEUROSURGICAL CONFERENCE

The First International Congress of Neurosurgery will be held in Brussels during the week of July 21–28, 1957 in conjunction with the International Congress of Neurological Sciences. Meeting jointly at that time will be the Sixth International Congress of Neurology, the Fourth International Congress of Electroencephalography, the Third International Congress of Neuropathology, the fifth meeting of the International League Against Epilepsy and the fifth meeting of the Symposium Neuroradiologicum.

During the first two days conjoint meetings